THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s):	Ream, et al.
Appl. No.:	09/990,628
Conf. No.:	4209
Filed:	November 13, 2001
Title:	OVER-COATED CHEWING GUM FORMULATIONS
Art Unit:	1615
Examiner:	S. Howard
Docket No.:	112703-203

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' APPEAL BRIEF

Sir:

Appellants submit this Appeal Brief in support of the Notice of Appeal filed on November 19, 2007. This Appeal is taken from the Final Rejection dated August 22, 2007.

I. REAL PARTY IN INTEREST

The real party in interest for the above-identified patent application on appeal is Wm. Wrigley Jr. Company by virtue of an Assignment dated October 11, 2001, October 17, 2001 and October 30, 2001 and recorded at the United States Patent and Trademark Office at reel 012321, frame 0775.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and the Assignee of the above-identified patent application note that there are no related appeals or interferences in this application.

III. STATUS OF CLAIMS

Claims 9-26 are pending in the above-identified patent application. Claims 9-26 are being appealed in this Brief. A copy of the appealed claims is provided in the Claims Appendix.

IV. STATUS OF AMENDMENTS

A Final Office Action was mailed on August 22, 2007. Appellants filed a Response to the Final Office Action on October 9, 2007. An Advisory Action was mailed on October 31, 2007. In the Advisory Action, the Response was considered but was deemed not to place the patent application in condition for allowance. A copy of the Final Office Action is attached as Exhibit A in the Evidence Appendix and a copy of the Advisory Action is attached as Exhibit B in the Evidence Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A summary of the invention by way of reference to the specification (a copy of which is attached as Exhibit C in the Evidence Appendix) for each of the independent claims (Claims 9 and 18) is provided as follows:

Independent Claim 9 is directed to a chewing gum (page 4, lines 10-20) comprising a gum center (page 4, lines 23-25 and page 15, line 5 to page 18, line 10); and a coating comprising a medicament that surrounds the gum center, the coating comprising at least 50% by weight of the chewing gum product, the medicament being designed to be delivered into the systemic system of a patient (page 1, lines 11-13; page 4, lines 25-27; page 5, lines 23-31, and page 9, lines 5-20).

Independent Claim 18 is directed to a product including a medicament that is designed to function by being delivered through the systemic system of an individual (page 1, lines 11-13; page 4, lines 9-10, and page 12, lines 5-16) comprising a chewing gum center (page 4, lines 23-25 and page 15, line 5 to page 18, line 10); and a coating that at least substantially surrounds the chewing gum center and comprises a medicament and a high-intensity sweetener, the coating comprising at least 50% by weight of the product (page 1, lines 11-13; page 4, lines 25-27; page 5, lines 23-31, and page 9, lines 5-20).

Although specification citations are given in accordance with C.F.R. 1.192(c), these reference numerals and citations are merely examples of where support may be found in the specification for the terms used in this section of the Brief. There is no intention to suggest in any way that the terms of the claims are limited to the examples in the specification. As demonstrated by the references numerals and citations below, the claims are fully supported by the specification as required by law. However, it is improper under the law to read limitations from the specification into the claims. Pointing out specification support for the claim terminology as is done here to comply with rule 1.192(c) does not in any way limit the scope of the claims to those examples from which they find support. Nor does this exercise provide a mechanism for circumventing the law precluding reading limitations into the claims from the specification. In short, the references numerals and specification citations are not to be construed as claim limitations or in any way used to limit the scope of the claims.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 9-26 stand rejected under 35 U.S.C. §103(a) as being obvious over the combination of U.S. Patent No. 4,317,838 to Cherukuri et al. ("*Cherukuri*") in view of WO 99/44436 to Stahl et al. ("*Stahl*"). A copy of *Cherukuri* is attached as Exhibit D in the Evidence Appendix. A copy of *Stahl* is attached as Exhibit E in the Evidence Appendix.

VII. ARGUMENT

A. LEGAL STANDARDS - Obviousness under 35 U.S.C. §103

The Federal Circuit has held that the legal determination of an obviousness rejection under 35 U.S.C. § 103 is:

> whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made…The foundational facts for the prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art…Moreover, objective indicia such as commercial success and long felt need are relevant to the determination of obviousness…Thus, each obviousness determination rests on its own facts.

In re Mayne, 41 U.S.P.Q. 2d 1451, 1453 (Fed. Cir. 1997).

In making this determination, the Patent Office has the initial burden of proving a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q. 2d 1955, 1956 (Fed. Cir. 1993). This burden may only be overcome "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings." *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). "If the examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 24 U.S.P.Q. 2d 1443, 1444 (Fed. Cir. 1992).

Moreover, the Patent Office must provide explicit reasons why the claimed invention is obvious in view of the prior art. The Supreme Court emphasized that when formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to "determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR v. Teleflex*, 550 U.S. __ (2007), 127 S.Ct. 1727.

Of course, references must be considered as a whole and those portions teaching against or away from the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve Inc.*, 796 F.2d 443 (Fed. Cir. 1986). "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the

path that was taken by the Applicant." *Monarch Knitting Machinery Corp. v. Fukuhara Industrial Trading Co., Ltd.*, 139 F.3d 1009 (Fed. Cir. 1998), quoting, *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994).

B. THE CLAIMED INVENTION

Independent Claim 9 is directed to a chewing gum comprising a gum center and a coating that surrounds the gum center. The coating comprises a medicament that is designed to be delivered into the systemic system of a patient. The coating comprises at least 50% by weight of the chewing gum.

Independent Claim 18 is directed to a product including a medicament. The product is designed to function by being delivered through the systemic system of an individual. The product comprises a chewing gum center and a coating that at least substantially surrounds the chewing gum center, comprising at least 50% by weight of the product. The coating comprises a medicament and a high-intensity sweetener.

Appellants have found that chewing a coated chewing gum with a medicament or agent in the coating, or in certain situations even placing the coated chewing gum in the mouth, releases the medicament or agent from the chewing gum. Continuing to chew the chewing gum creates a pressure within the buccal cavity forcing the agent or medicament directly into the systemic system of the individual through the oral mucosa contained in the buccal cavity. This greatly enhances the absorption of the medicament or agent into the systemic system of the individual as well as the bioavailability of the medicament or agent within the system.

Appellants have also found that an increase in the absorption of the medicament or agent through the oral mucosa is achieved when compared to typical oral administration. In other words, the medicament or agent is absorbed into the system of an individual more quickly through the oral mucosa than if it was swallowed as in a typical oral administration. Indeed, the absorption of the medicament or agent through the oral mucosa approaches that of a parental administration (e.g. intravenous or intramuscular injection), and bioavailability is also much greater than oral administration. Teachings and examples in the specification supporting and elucidating the scope of the present invention include page 1, lines 11-13; page 4, lines 9-20 and 23-25; page 5, lines 23-31; page 9, lines 5-20; page 12, lines 5-16, and page 15, line 5 to page 18, line 10.

C. THE REJECTION OF CLAIMS 9-26 SHOULD BE REVERSED BECAUSE THE PATENT OFFICE HAS FAILED TO ESTABLISH A PRIMA FACIE CASE OF OBVIOUSNESS

The Examiner asserts that the combination of *Cherukuri* and *Stahl* renders obvious Claims 9-26. Independent Claims 9 and 18 recite, in part, a product comprising a gum center and a coating comprising at least 50% by weight of the chewing gum product. In contrast, Appellants respectfully submit that *Cherukuri* and *Stahl* are deficient with respect to elements of Claims 9-26 as detailed below.

Cherukuri is directed to a so-called "one step" or "one syrup" method for providing a sugarless coating on a solid center, which includes applying alternating layers of coating syrup and dusting mix. See, *Cherukuri*, column 2, lines 14-30. As a result, rather than teaching overall coating levels, *Cherukuri* emphasizes the components of the coating syrup and dusting mix as well as specific ingredient percentages within the coating syrup and dusting mix. See, *Cherukuri*, column 2, lines 40-55 and column 3, line 51 to column 4, line 4. If fact, none of the weight percentages disclosed teach a coating comprising at least 50% by weight of the overall product. Instead, the highest, and only, coating level disclosed in *Cherukuri* is 35 weight percent of the coated chewing gum tablet. See, *Cherukuri*, column 4, lines 29-34 and column 7, lines 13-19. Therefore, as admitted in the Office Action dated August 22, 2007 (refer to Exhibit A), *Cherukuri* fails to disclose or suggest a coating comprising at least 50% by weight of the chewing gum product as required, in part, by Claims 9 and 18.

However, in the Advisory Action dated October 31, 2007 (refer to Exhibit B), the Examiner asserts that column 4, lines 29-34 of *Cherukuri* teaches one skilled in the art how to obtain at least 50% by weight coating since *Cherukuri* clearly teaches that 10-12 coats of coating syrup and 7-9 coats of dusting mix are required for 35% by weight of chewing gum. Based on these numbers, the Examiner asserts that one skilled in the art, by routine experimentation, could calculate the number of sugar coatings and dusting mixes required to achieve the at least 50% by weight coating of the present claims, and then apply that number of syrup and dusting coats. Appellants respectfully disagree and respectfully submit that one having skill in the art would have no reason, in view of *Cherukuri*, to increase the coating level from a typical level of 35% to the presently claimed coating level of at least 50%.

The present claims provide improved products for delivering a medicament or agent to an individual. To this end, chewing gum, specifically a coated chewing gum product, is provided including a medicament or agent. The medicament or agent is present within the coating. The coating substantially encloses a gum center (the water soluble portion and insoluble base portion) and comprises at least 50% by weight of the product. In other words, the coating comprising the medicament must have a weight equal to or greater than that of the gum center.

By having a coating comprising at least 50% by weight of the entire chewing gum product, a larger amount of medicament or agent can be placed in the coating. As a result, chewing the gum releases more medicament or agent into the saliva in higher concentrations. See, specification, page 12, lines 22-24. A higher concentration of medicament or agent in the saliva results in a higher concentration gradient in the oral cavity. This improves absorption of the medicament or agent through the oral mucosa. See, specification, page 9, lines 5-20.

Moreover, in contrast to typical coated chewing gum products, the products of the present invention include an increased coating level of at least 50% by weight coating. See, specification, page 13, lines 27-28. This increased coating level also allows certain medicaments to achieve high enough levels to perform an intended medicinal purpose. Further, this high coating level allows the coating to function as a masking agent. See, specification, page 14, lines 1-8.

In contrast to the above, one skilled in art would have no reason, in view of *Cherukuri*, to increase the coating level from the typical level of 35% to the "over-coated" level of at least 50%. As stated above, the claims require a coated chewing gum where the coating comprising the medicament must have a weight equal to or greater than that of the gum center. It would clearly be out of the norm to have a coated chewing gum with more coating than actual chewing gum. As a result, it is essential to establish a reason to achieve such a high level of coating.

As stated previously, *Cherukuri* is directed to a so-called "one step" or "one syrup" method for providing a sugarless coating on a solid center which includes applying alternating layers of coating syrup and dusting mix. When that solid center is a coated chewing gum, *Cherukuri* states that 10-12 coats of coating syrup and 7-9 coats of dusting mix may be required, as asserted by the Examiner above, to achieve a 35% by weight coating. *Cherukuri* also teaches that the number of applications will also vary depending on the amount of solids present in the

coating syrup, the amount of dusting mix employed, and the type of comestible to be coated. See, *Cherukuri*, column 4, lines 35-39.

However, *Cherukuri* already teaches a specific coating procedure and coating level (35%) for coated chewing gum. Moreover, *Cherukuri* fails to teach that the weight percentage of coating can vary from this established level for coated chewing gum. Instead, *Cherukuri* teaches that the number of applications can vary based on factors such as amount of solids in the coating syrup. Using the above teachings in *Cherukuri*, if the solids level in a coating syrup is low, the number of coating syrup applications can increase to meet the 35 weight % established form coating in a coated chewing gum. However, this still does not teach or provide any reason for increasing the overall coating weight percentage above the 35% that *Cherukuri* establishes for a coated chewing gum. Moreover, *Cherukuri* does not teach medicament or agent use in the coating as a reason for varying the number of coating syrup/dusting mix applications. Therefore, *Cherukuri* provides no reason why one skilled in the art would increase the weight percentage of coating in a chewing gum from 35% to at least 50%.

Accordingly, though the Examiner asserts that routine experimentation would lead one skilled in the art to achieve the at least 50% by weight coating in view of the teaching in *Cherukuri*, the Examiner clearly does not establish a reason why one skilled in the art would want to achieve the at least 50% by weight coating of the present claims.

Stahl also fails to disclose or suggest a coating comprising at least 50% by weight of the product as required, in part, by independent Claims 9 and 18. Instead, the Examiner relies upon *Stahl* for arguably teaching a medicament in the coating along with a sweetener, an element the Office Action admits *Cherukuri* lacks.

Appellants have found that chewing a coated chewing gum with a medicament or agent in the coating, or in certain situations even placing the coated chewing gum in the mouth, releases the medicament or agent from the chewing gum. Continuing to chew the chewing gum creates a pressure within the buccal cavity forcing the agent or medicament directly into the systemic system of the individual through the oral mucosa contained in the buccal cavity. This greatly enhances the absorption of the medicament or agent into the systemic system of the individual as well as the bioavailability of the medicament or agent within the system. See, specification, page 9, lines 5-20 (Exhibit C).

Appellants have also found that an increase in the absorption of the medicament or agent through the oral mucosa is achieved when compared to typical oral administration. In other words, the medicament or agent is absorbed into the system of an individual more quickly through the oral mucosa than if it was swallowed as in a typical oral administration. Indeed, the absorption of the medicament or agent through the oral mucosa approaches that of a parental administration (e.g. intravenous or intramuscular injection), and bioavailability is also much greater than oral administration. See, specification, page 9, lines 5-20 and page 11, lines 29-31 (Exhibit C).

In sum, *Cherukuri* and *Stahl* fail to disclose or suggest every element of the present claims and fail to even recognize the advantages, benefits and/or properties of a consumable product having coating comprising at least 50% by weight of the product in accordance with the present claims.

For at least the reasons discussed above, the combination of *Cherukuri* and *Stahl* fails to teach, suggest, or even disclose all of the elements of Claims 9 and 18 and Claims 10-17 and 19-26 that depend from Claims 9 and 18, and thus, fail to render the claimed subject matter obvious.

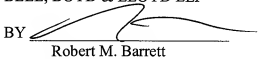
VIII. CONCLUSION

Appellants further submit that the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. §103(a) with respect to the rejection of Claims 9-26. Accordingly, Appellants respectfully submit that the obviousness rejection is erroneous in law and in fact and should therefore be reversed by this Board.

The Director is authorized to charge any fees that may be required, or to credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 112703-203 on the account statement.

Respectfully submitted,

BELL, BOYD & LLOYD LLP

BY 

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Dated: January 18, 2008

CLAIMS APPENDIX

PENDING CLAIMS ON APPEAL OF U.S. PATENT APPLICATION SERIAL NO. 09/990,628

9. A chewing gum comprising:

a gum center; and

a coating comprising a medicament that surrounds the gum center, the coating comprising at least 50% by weight of the chewing gum product, the medicament being designed to be delivered into the systemic system of a patient.

10. The chewing gum of Claim 9 wherein the medicament is selected from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; stimulants; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

11. The chewing gum of Claim 9 wherein the coating includes a sufficient amount of taste masking agent to provide acceptable organoleptic properties.

12. The chewing gum of Claim 11 wherein the taste masking agent is selected from the group consisting of: zinc gluconate, ethyl maltol, glycine, acesulfame-k, aspartame; saccharin; fructose; xylitol; isomalt; maltitol; spray dried licorice root; glycerrhizine; sodium gluconate; glucono delta-lactone; ethyl vanillin; dextrose; sucralose; vanillin; and ethyl maltol.

13. The chewing gum of Claim 11 wherein the taste masking agent comprises approximately 30% to about 99% by weight of the coating.

14. The chewing gum of Claim 9 wherein the coating includes approximately 0.5% to about 5% by weight of a high-intensity sweetener chosen from the group consisting of aspartame, sucralose, saccharine, and acesulfame-k.

15. The chewing gum of Claim 9 wherein the gum center includes at least 50% by weight water-insoluble gum base.

16. The chewing gum of Claim 9 wherein the coating does not have a shellac layer.

17. The chewing gum of Claim 9 wherein the gum center and coating are sugar-free.

18. A product including a medicament that is designed to function by being delivered through the systemic system of an individual comprising:

a chewing gum center; and

a coating that at least substantially surrounds the chewing gum center and comprises a medicament and a high-intensity sweetener, the coating comprising at least 50% by weight of the product.

19. The product of Claim 18 wherein the medicament is selected from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; stimulants; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

20. The product of Claim 18 wherein the coating includes a sufficient amount of taste masking agent to provide acceptable organoleptic properties.

21. The product of Claim 18 wherein the taste masking agent is selected from the group consisting of: zinc gluconate, ethyl maltol, glycine, acesulfame-k, aspartame; saccharin; fructose; xylitol; isomalt; maltitol; spray dried licorice root; glycerrhizine; sodium gluconate; glucono delta-lactone; ethyl vanillin; dextrose; sucralose; vanillin; and ethyl maltol.

22. The product of Claim 18 wherein the taste masking agent comprises approximately 30% to about 99% by weight of the coating.

23. The product of Claim 18 wherein the coating includes approximately 0.5% to about 5% by weight of a high-intensity sweetener chosen from the group consisting of aspartame, sucralose, saccharine, and acesulfame-k.

24. The product of Claim 18 wherein the coating comprises at least 70% by weight powder when it is applied to the gum center.

25. The product of Claim 18 wherein the product is sugar-free.

26. The product of Claim 18 wherein the coating does not have a shellac layer.

EVIDENCE APPENDIX

EXHIBIT A: Final Office Action mailed on August 22, 2007.

EXHIBIT B: Advisory Action mailed on October 31, 2007.

EXHIBIT C: Original Specification

EXHIBIT D: U.S. Patent No. 4,317,838 to Cherukuri et al. ("*Cherukuri*")

EXHIBIT E: WO 99/44436 to Stahl et al. ("*Stahl*")

Exhibit A

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,628	11/13/2001	Ronald L. Ream	112703-203	4209

29156 7590 08/22/2007

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EXAMINER	
VENKAT, JYOTHSNA A	
ART UNIT	**PAPER NUMBER**
1615	
MAIL DATE	**DELIVERY MODE**
08/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,628	REAM ET AL.	
	Examiner	Art Unit	
	JYOTHSNA A. VENKAT Ph. D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of amendment filed on 6/7/07.

Claims 9- 26 are pending in the application and the status of the application is as follows:

Claim Rejections - 35 USC § 103

Claims 9-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of U. S. Patent 4,317,838('838) and WO 99/44436 ('436).

Patent '838 teaches method for applying coating to chewing gum. See the abstarct, see col.2, lines 35-68, wherein the patent teaches coating syrup using sweeteners or bulking agents. This is same as claimed taste masking agent. Patent at col.2, lines 40-55 teaches that sweeteners to be coated using various ingredients. This range disclosed in the patent for coating meets the claimed requirement of " coating comprising at least 50% of the chewing gum product". Patent at col.5, lines 10-19 teaches claimed high-intensity sweeteners. Patent at col.5, lines 6-8 teach that the high-intensity sweetener can be present in the gum base or in the coating Patent at col.5, lines 29-31 teach gum base and the amount present by weight. Patent at col.5, lines 55-60 suggests, " in addition to chewing gum, the comestibles to be coated may include... other dosage forms for medicinal or therapeutic use". Medicinal are same as medicaments. Thus patent clearly suggests to one of ordinary skill in the art that coating can also include medicaments. The difference between the patent and the instant application is patent does not have medicament in the coating along with sweetener. However, WO '436 teaches coated chewing gum comprising a core of chewing gum and a coating comprising a coating material and one or more active substances. See the abstarct, see page 1 under " technical field", see also page 2. WO document at page 3, last paragraph teaches active ingredients, which can be sweeteners. WO document at

page 8, lines 15-17 teaches claimed high-intensity sweeteners. See also page 8, lines 20-24 wherein WO document teaches that along with active substances other functional groups can also be incorporated. These functional groups include vitamins and nutrients along with various pharmaceuticals, which are described at paragraph bridging pages 9-10. WO document at page 12 first paragraph teaches that the coating suspension comprise aqueous solution of xylitol, maltitol, isomalt, aspartame, acesulfame K and saccharin. These ingredients are claimed as taste masking agent.

Accordingly it would have been obvious to one of ordinary skill in the art to make to prepare gum base (gum center) and coat the gum base using taste masking agent and high intensity sweetener taught by patent '838 and include in the coating medicament taught by WO '436 in analogous coated chewing gum preparations. The idea of adding medicament into the coating flows logically from the art since one prior art teaches chewing gum coating using taste masking agent and high intensity sweetener and another prior art teaches chewing gum coating using active substances (high intensity sweetener), functional substances (medicaments) or sugar or sugar alcohols (taste masking agent). One of ordinary skill in the art would be motivated to coat the gum center with a medicament along with taste masking agent with the reasonable expectation of success that having medicament in the coating provides a better stability of the active substance (medicament) and increased effect there of in all chewing phases. This is a prima facie case of obviousness.

Response to Arguments

Applicant's arguments filed 6/7/07 have been fully considered but they are not persuasive.

Applicants argue:

"For example, Cherukuri fails to disclose or suggest a coating comprising at least 50% by weight of the product. Though the Patent Office alleges that Cherukuri does indeed disclose this limitation (see, Office Action, page 2), none of the weight percentages disclosed teach a coating comprising at least 50% by weight of the overall product. See, for example, Cherukuri, column 2, lines 40-55 ("by weight of the coating syrup"); column 3, line 50 - column 4, line 4 ("by weight of the dusting mix"); column 4, lines 50-55 ("by weight of the gum center"); column 4, lines 55-58 ("by weight of the coating"), and column 5, lines 43-47 ("by weight of the gum base"). Moreover, when actually referring to weight % coating in the total product, Cherukuri only discloses a level of 35% by weight coating in the coated chewing gum tablet. See, Cherukuri, column 4, lines 29-34 and column 7, lines 15-19".

In response to the above argument applicant's attention is drawn to claim 9. See claim 9 below:

Claim 9 (currently amended): A chewing gum comprising: a gum center; and a coating comprising including a medicament that surrounds the gum center, the coating comprising at least 50% by weight of the chewing gum product, the medicament being designed to be delivered into the systemic system of a patient.

Thus the claimed chewing gum product has the gum center and coating that surrounds the gum center and the coating comprising at least 50% by weight of the chewing gum product. Specification at page 15 teaches, " *pursuant to the present invention, the gum center may be based on a variety of different chewing gums that are known. For example, the gum center can*

be low or high moisture, sugar or sugarless, wax containing or wax free, low calorie (via high base or low calorie bulking 10 agents), and/or may contain dental agents". Gum center has gum base and sugar See gum center at page 18 of the specification. Patent '838 also teaches gum center using gum base and sugar. See table 1 of patent. Patent at col.4, lines 25-29 teaches that the application of coating syrup and dusting mix are continued until the average gum piece weight reaches about 90% of the required coated weight. This meets claimed limitation of "the coating comprising at least 50% by weight of the chewing gum product".

Applicants also argue:

" Stahl (WO document) fails to remedy the deficiencies of Cherukuri. The Patent Office relies upon Stahl for arguably teaching a medicament in the coating along with a sweetener, an element the Office Action admits Cherukuri lacks. See, Office Action, page 3. Therefore, Stahl, like Cherukuri, still fails to disclose or suggest a coating comprising at least 50% by weight of the product".

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In conclusion, one of ordinary skill in the art would be motivated to coat the gum center with a medicament along with taste masking agent with the reasonable expectation of success that having medicament in the coating provides a better stability of the active substance (medicament) and increased effect there of in all chewing phases.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JYOTHSNA A. VENKAT Ph. D whose telephone number is 571-272-0607. The examiner can normally be reached on Monday-Friday, 10:30-7:30:1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL WOODWARD can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JYOTHSNA A VENKAT Ph. D
Primary Examiner
Art Unit 1615

***

Exhibit B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,628	11/13/2001	Ronald L. Ream	112703-203	4209

29156 7590 10/31/2007

BELL, BOYD & LLOYD LLP
P.O. Box 1135
CHICAGO, IL 60690

EXAMINER	
VENKAT, JYOTHSNA A	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/990,628	REAM ET AL.	
	Examiner	Art Unit	
	JYOTHSNA A. VENKAT Ph. D	1615	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 October 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 9-26.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See Continuation Sheet.

12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

J. Venkat

JYOTHSNA A VENKAT Ph. D
Primary Examiner
Art Unit: 1615

Continuation of 11. does NOT place the application in condition for allowance because: Applicants argue that patent '838 discloses only 35 % by weight of coating at col.4, ll 29-34 and col.7, ll 15-19 and applying 10-12 coats of coating syrup and 7-9 coats of dusting achieve 90% of the required 35% by weight of coating and the patent fails to disclose the claimed coating of at least 50% by weight of the product. In response to this argument, patent at col.4, ll, 29-34 teaches one skilled in the art how to obtain at least 50% by weight since patent clearly teaches to one skilled in the art that 10-12 coats of coating syrup and 7-9 coats of dusting mix are required for 35% by weight of chewing gum and more coats of syrup and more coats of dusting mix are needed for coating of at least 50% by weight claimed in instant application. Routine optimization is within the ken of the skilled chemist, since one skilled in the art would calculate the number of sugar coatings and number of dusting mix required to achieve at least 50 % by weight of the products from patent '838 at col.4, ll 29-34 .

Exhibit C

SPECIFICATION

TITLE OF INVENTION

"OVER-COATED CHEWING GUM FORMULATIONS"

This is a continuation of U.S. Patent Application No. 09/510,878, filed February 23, 2000, which is a continuation-in-part of U.S. Patent Application Serial Nos. 09/286,818, filed on April 6, 1999 and PCT Patent Application No. PCT/US99/29742 filed on December 14, 1999.

BACKGROUND OF THE INVENTION

The present invention generally relates to the delivery of medicaments and other agents. More specifically, the present invention relates to the delivery of medicaments and agents using chewing gum formulations.

It is of course known to provide agents to individuals for various purposes. These agents can be used to treat diseases and as such are typically referred to as drugs or medicaments. Likewise, the drugs or medicaments can be used for prophylactic purposes. Still, it is known to provide agents to an individual for a variety of non-medical purposes including enhancing performance or maintaining or initiating alertness.

There are a great variety of such agents. These agents run the gamut from stimulants such as caffeine to drugs such as analgesics, tranquilizers, cardiovascular products, insulin, etc. Some such agents are taken on an as needed basis while other agents must be taken at regular intervals by the individual.

Typically, drugs (medicaments) are administered parenterally or enterally. Of course, parenteral administration is the administration of the drug intravenously directly into the blood stream. Enteral refers to the administration of the drug into the gastrointestinal tract. In either case, the goal of the drug administration is to move the drug from the site of administration towards the systemic circulation.

Except when given intravenously, a drug must traverse several semipermeable cell membranes before reaching general circulation. These membranes act as a biological barrier that inhibits the passage of drug molecules. There are believed to be four processes by which drugs move across a biological barrier: passive diffusion; facilitated diffusion; active transport; and pinocytosis.

Passive diffusion is the transport across the cell membrane wherein the driving force for the movement is the concentration gradient of the solute. In orally administered drugs, this absorption occurs in the small intestines. Facilitated diffusion is believed to be based on a carrier component that combines reversibly with the substrate molecule at the cell membrane exterior. The carrier substrate complex diffuses rapidly across the membrane with release of the substrate at the interior surface. Active transport requires an energy expenditure by the cell and appears to be limited to agents with structural similarities to normal body constituents. These agents are usually absorbed from specific sites in the small intestines. Pinocytosis refers to the engulfing of particulars or fluid by a cell. It is believed to play a minor role in drug transport. *Merck Manual*, 16th Edition, pp. 2598-2599.

In determining the efficacy of a drug and the effectiveness of the use of a drug to treat a disease, drug absorption is a critical concern. Drug absorption refers to the process of drug movement from the site of administration toward the systemic circulation.

Oral administration of drugs is by far the most common method. When administered orally, drug absorption usually occurs due to the transport of cells across the membranes of the epithelial cells within the gastrointestinal tract. Absorption after oral administration is confounded by numerous factors. These factors include differences down the alimentary cannel in: the luminal pH; surface area per luminal volume; perfusion of tissue, bile, and mucus flow; and the epithelial membranes. See *Merck Manual* at page 2599.

A further issue effecting the absorption of orally administered drugs is the form of the drug. Most orally administered drugs are in the form of tablets or capsules. This is primarily for convenience, economy, stability, and patient acceptance. Accordingly, these capsules or tablets must be disintegrated or dissolved before absorption can occur. There are a variety of factors capable of varying or retarding disintegration of solid dosage forms. Further, there are a variety of factors that effect the dissolution rate and therefore determine the availability of the drug for absorption. See *Merck Manual* at page 2600.

Parental administration allows for the direct placement of the drug into the blood stream. This usually insures complete delivery of the dose to the general circulation. However, administration by a route that requires drug transfer through one

or more biologic membranes to reach the blood stream precludes a guarantee that all of the drug will eventually be absorbed. Even with parental administration, because capillaries tend to be highly porous, the perfusion (blood flow/gram of tissue) is a major factor in the rate of absorption. Thus, the injection site can markedly influence a drugs' absorption rate; e.g., the absorption rate of diazepam injected IM into a site with poor blood flow can be much slower than following an oral dose. See *Merck Manual* at page 2601.

Not only is drug absorption an issue in drug delivery but also the bioavailability of the drug is also critical. Bioavailability is defined as the rate at which and the extent to which the active moiety (drug or metabolite) enters the general circulation, thereby gaining access to the site of action. Bioavailability depends upon a number of factors, including how a drug product is designed and manufactured, its physicochemical properties, and factors that relate to the physiology and pathology of the patient. See *Merck Manual* at page 2602.

When a drug rapidly dissolves from a drug product and readily passes across membranes, absorption from most site administration tends to be complete. This is not always the case for drugs given orally. Before reaching the vena cava, the drug must move down the alimentary cannel and pass through the gut wall and liver, which are common sites of drug metabolism. Thus, the drug may be metabolized before it can be measured in the general circulation. This cause of a decrease in drug input is called the first pass effect. A large number of drugs show low bioavailability owing to an extensive first pass metabolism. The two other most frequent causes of low bioavailability are insufficient time in the GI tract and the presence of competing reactions. See *Merck Manual* at page 2602.

Bioavailability considerations are most often encountered for orally administered drugs. Differences in bioavailability can have profound clinical significance.

Although parental administration does provide a method for eliminating a number of the variables that are present with oral administration, parental administration is not a preferable route. Typically, parental administration requires the use of medical personnel and is just not warranted nor practical for the administration of most agents and drugs, e.g., analgesics. Even when required parenteral administration is not preferred due to patient concerns including comfort, infection,

etc., as well as the equipment and costs involved. However, despite best efforts certain therapies require parenterally injected drugs. For example, research for decades has focused on an attempt to deliver insulin to an individual through a non-parental means. Despite such efforts today insulin is still only administered intravenously.

There is therefore a need for an improved method of delivering drugs and agents to an individual.

SUMMARY OF THE INVENTION

The present invention provides improved methods for delivering a medicament or agent to an individual. To this end, chewing gum, specifically a coated chewing gum product, is provided including a medicament or agent. The medicament or agent is present within the coating or shell that substantially encloses a gum center (the water soluble portion and insoluble base portion). It has been found that by chewing the overcoated chewing gum, or in certain situations even placing the coated chewing gum in the mouth, the medicament or agent is released from the chewing gum. Continuing to chew the chewing gum, it is believed, creates a pressure within the buccal cavity forcing the agent or medicament directly into the systemic system of the individual through the oral mucosa contained in the buccal cavity. This greatly enhances the absorption of the drug into the systemic system as well as the bioavailability of the drug within the system.

Improved formulations including medicaments or agents are also provided by the present invention.

To this end, the present invention provides a coated chewing gum composition including a gum center. The gum center includes a water soluble portion and a water insoluble portion. A coating substantially surrounds the gum center, the coating comprises at least 50% by weight of the chewing gum product. The product includes a medicament or agent.

In an embodiment, the coating includes a sufficient amount of a masking agent to improve the organoleptic properties of the coating containing the medicament. The masking agent may be chosen from the group consisting of: sucralose; zinc gluconate; ethyl maltol; glycine; acesulfame-K; aspartame; saccharin; fructose; xylitol; spray dried licorice root; glycerrhizine; dextrose; sodium gluconate; glucono delta-lactone; ethyl

vanillin; vanillin; normal and high-potency sweeteners; and a variety of appropriate flavors.

In an embodiment, the coating includes a high-intensity sweetener. In a further embodiment, the high-intensity sweetener is chosen from the group consisting of aspartame, sucralose, and acesulfame-K.

In an embodiment, the gum center comprises approximately 30% to about 90% by weight water insoluble gum base.

In an embodiment, the formulation creates a saliva content of medicament of at least 5 ppm to about 66% medicament by weight in the saliva, depending on the medicament.

In an embodiment, the coating comprises up to 75% by weight of the chewing gum composition.

In an embodiment, the coating is a recrystallized granular coating.

In an embodiment, the coating is an amorphous coating.

In an embodiment, the coating is a powder coating.

In an embodiment, the chewing gum is chewed for at least 2 minutes.

In an embodiment, the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antacids; antihistamines; decongestants; anti-inflammatories; antibiotics; antivirals; psychotherapeutic agents; insulin; and cardiovascular agents.

In an embodiment, the chewing gum including the medicament is chewed at least twice a day.

In an embodiment, two pieces of chewing gum are chewed at a time.

In another embodiment of the present invention a method of drug delivery is provided. The method comprising the steps of: providing a chewing gum that includes a coating that comprises at least 50% by weight of the chewing gum, the coating including a medicament that substantially surrounds a gum center; chewing the chewing gum to cause the medicament to be released from the chewing gum composition into the buccal cavity of the chewer; and continuing to chew the chewing gum thereby creating a fluid pressure causing the medicament to enter the systemic system of the chewer through the oral mucosa contained in the buccal cavity.

In a further embodiment of the present invention, a method for reducing the amount of agent necessary to achieve an effect in an individual as compared to a typical

agent that is swallowed is provided. The method comprises the steps of: providing a chewing gum including a coating that surrounds a gum center, the coating comprising at least 50% by weight of the total chewing gum, the coating including an agent that is typically swallowed by an individual to achieve a specific effect. However, the coating includes less than the typical amount of agent that is swallowed by the individual to achieve the effect; chewing the chewing gum and thereby causing the agent to be released into the salvia of the individual; and continuing to chew the chewing gum forcing the agent through the mucous membranes in a buccal cavity of the individual.

In an embodiment of the method, the agent is a medicament. In an embodiment of the method, the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antihistamines; decongestants; antacids; anti-inflammatories; antibiotics; antivirals; psychotherapeutic agents; and cardiovascular agents.

In an embodiment of the method, the chewing gum is chewed for at least 2 minutes.

In an embodiment of the method, the chewing gum creates a saliva content of agent of at least 0.5 to about 5000 ppm depending on the medicament.

In an embodiment of the method, the agent is a stimulant.

In a still further embodiment of the present invention, a method of enhancing an individual's performance is provided. The method comprising the steps of: providing chewing gum including a performance enhancing amount of caffeine in a coating that surrounds a chewing gum center, the coating comprising at least 50% by weight of the chewing gum; and chewing the chewing gum not more than ten minutes before the performance.

In an embodiment, the performance to be enhanced is athletic.

In an embodiment, the performance to be enhanced is cognitive.

In an embodiment, the performance to be enhanced is alertness.

In an embodiment, the chewing gum is chewed not more than 5 minutes before the performance.

In yet another embodiment of the present invention a method of delivering a medicament is provided. The method comprising the steps of: providing a chewing gum including a coating that comprises at least 50% by weight of the chewing gum and surrounds a gum center and includes a medicament; and chewing the chewing gum for at least 2 minutes.

Yet further, in an embodiment of the present invention a method of increasing the stimulatory effect of a stimulant that has been previously ingested by an individual is provided. The method comprising the steps of: providing a chewing gum that includes a coating that contains a stimulant and surrounds a gum center the coating comprising at least 50% by weight of the chewing gum; and chewing the chewing gum causing the stimulant to be released by the chewing gum and forced into the oral mucosa of the individual.

In a still further embodiment of the present invention a chewing gum composition is provided. The chewing gum includes a gum center including a water soluble portion and a water insoluble portion, the water insoluble portion comprising at least 30% by weight of the gum center. The coating surrounds the center and includes a medicament and comprising at least 50% by weight of the chewing gum. The coating includes a macrosweetener.

Moreover, in an embodiment of the present invention, a method of manufacturing a medicament containing product is provided. The method comprising the steps of: preparing a gum center having water-soluble portion and a water-insoluble; coating the center with a powder and a syrup to create a coated product, at least one of the powder or syrup portion including a medicament; and the coated product comprising at least 50% by weight syrup and powder coating. The powder and syrup are coated on the gum center in alternating steps until a sufficient coating has been built up. Preferably the coating is not covered with a shellac or other finishing layer but rather maintains a matte finish.

Accordingly, an advantage of the present invention is to provide new methods for delivering medicaments or agents to an individual.

Furthermore, an advantage of the present invention is to provide an improved product containing a medicament.

Still further, an advantage of the present invention is to provide a method of delivering medicaments to an individual that provides for increase absorption and bioavailability as compared to medicaments that are designed to be absorbed in the GI tract.

Further, an advantage of the present invention is to provide a method of administering a medicament or agent to an individual at a lower level than is typically administered orally while still achieving the same effect.

Furthermore, an advantage of the present invention is to provide a method for administering medicaments or agents to an individual that heretofore were administered parentally.

Additionally, an advantage of the present invention is to provide a method for administering medicaments that is more palatable than current methods.

Another advantage of the present invention is to provide a method for enhancing the performance of an individual through the administration of an agent.

Moreover, an advantage of the present invention is to provide an improved method for drug delivery.

Still, an advantage of the present invention is to provide a method for creating a triggering effect that creates a synergistic effect with an agent that is present in the systemic circulation of the individual.

An advantage of the present invention is that a coated product is provided wherein the coating can absorb or lose moisture without apparent degradation.

Further, an advantage of the present invention is that a coated chewing gum product including medicament is provided having an extended shelf-life.

Additional features and advantages of the present invention will be described in and apparent from the detailed description of the presently preferred embodiments and the figures.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates generally an embodiment of the chewing gum of the present invention.

Figure 2 illustrates graphically the results of Experiment No. 1 that is discussed supra.

Figure 3 illustrates graphically the results of Experiment No. 2 that is discussed supra.

Figure 4 illustrates graphically the results of Experiment No. 3 that is discussed supra.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved methods for delivering medicaments and other agents to an individual as well as improved products including such medicaments or agents.

Pursuant to the present invention, a medicament or agent is contained in a coating that surrounds a gum center formulation. The coating comprises at least 50% by weight of the entire chewing gum product. As the chewing gum is chewed, the medicament or agent is released into the saliva. During continual chewing, the medicament or agent in the saliva is then forced through the oral mucosa in the buccal cavity due to the pressure created by the chewing. The oral mucosa has a thin epithelium and a rich vascularity. Thus, the oral mucosa favors drug absorption. In contrast to a typically orally ingested drug, wherein the solution is in contact too briefly for absorption to be appreciable through the oral mucosa, it is believed that during chewing, the agent and/or medicament remains in the buccal cavity and is forced through the oral mucosa. Also it has been surprisingly found that an increase in the absorption of the drug is achieved as well as an increase in the bioavailability of the drug as compared to typical oral administration. It has been found that the drug or agent is absorbed much quicker than if it was swallowed as in a typical oral administration. Indeed, the absorption approaches that of a parental administration, and bioavailability is also much greater than oral administration.

Referring to Figure 1, an embodiment of the chewing gum composition 10 of the present invention is illustrated. As illustrated, the chewing gum composition 10 includes a gum center 12. The gum center can be any chewing gum formulation known in the art, though as noted below preferably the gum center has a higher level of water insoluble gum base than is typically used. Pursuant to the present invention, surrounding the gum center 12 is a coating 14. The coating 14 includes a medicament or other active agent.

Referring now to the coating 14, the coating 14 comprises at least 50% by weight of the chewing gum composition. Preferably, the coating comprises approximately 50% to about 75% by weight of the chewing gum composition and in a preferred embodiment, the coating comprises approximately 67% by weight of the product. A variety of coatings can be utilized. For example, the coating can be a soft amorphous coating. Or, the coating can be a recrystallized granular coating. As

discussed below, in a preferred embodiment, the coating is applied as a syrup/powder composition.

Preferably, the coating will include masking agents. In this regard, high-intensity sweeteners and appropriate flavors can be used to mask any off notes that are present due to the medicament or agent. It has been found that with respect to certain medicaments or agents that may have an astringent or bitter taste that by adding a masking agent to the formulation, that a much more palatable formulation, including the medicament, can be provided. In this regard, even though the medicament in for example, its powder form may be bitter or have an offensive taste, the matrix used as the coating of the present invention, including the masking agent, will afford a product having acceptable organoleptic properties. For example, it has been surprisingly found that by solubilizing a powdered matrix of medicament and masking agent, this increases the ability of the masking agent to cover up bitter and bad flavors produced by the medicament or agent. By selecting specific masking agents based on the bad or off taste produced by the medicament, one can provide a palatable formulation.

For example, if one is attempting to cover an astringent flavor such as aspirin, one could use masking agents found to be effective against astringency such as fructose and high-intensity sweeteners, e.g. saccharin, aspartame, sucralose, and acesulfame-k. In the case of a moderately bitter active ingredient, such as caffeine, one would use ingredients such as glycine, ethyl maltol, zinc gluconate, licorice root powder, high-intensity sweeteners, etc. In the case of a very bad tasking active ingredient such as acetaminophen it has been found that peppermint functions very well, but, may need to be augmented with a high-intensity sweetener, such as, for example, aspartame.

The masking agents, in an embodiment, are selected from the group consisting of: sucralose; zinc gluconate; ethyl maltol; glycine; acesulfame-k; aspartame; saccharin; fructose; xylitol; maltitol; isomalt; salt; spray dried licorice root; glycyrrhizin; dextrose; sodium gluconate; sucrose; glucono delta-lactone; ethyl vanillin; and vanillin.

In an embodiment of the invention, sufficient masking agent will be used in the coating to improve and provide acceptable organoleptic properties to the chewing gum product. As used herein to provide "acceptable organoleptic properties" means that the chewing gum formulation will have a sufficiently pleasant, or at least non-offensive

taste, to allow the consumer to chew the chewing gum for at least two minutes. Whether a masking agent is necessary and/or the amount of masking agent will vary depending on medicament or agent. Of course, if desired, more than one masking agent can be used, e.g., zinc gluconate and a sweetener or flavor. In an embodiment, the masking agent may comprise approximately 30% to about 99% by weight of the coating formulation.

In a preferred embodiment, the coating includes a high-intensity sweetener such as aspartame, sucralose, and acesulfame-k. Preferably, the high-intensity sweetener comprises approximately 0.5% to about 5% by weight of the coating.

As noted above, the coating will include a medicament or agent. It has also been surprisingly found that less medicament or agent can be placed in the chewing gum than is typically orally administered to an individual to achieve an effect and the same bioequivalence can be achieved. In fact, it has been surprisingly found that in certain instances, for at least certain drugs and agents, the administration of the medicament or agent using chewing gum through the buccal cavity can provide an increase effect even as compared to parenteral administration.

For example, caffeine is commonly used as a stimulant to alleviate the effects of sleep deprivation. It is almost completely metabolized in the liver and therefore classified as a low clearance, flow independent drug. This means its rate of inactivation is unaffected by delivery to the liver and can only be modified by a change in the hepatic enzyme activity.

The pharmacokinetics of caffeine have been well documented and there is no significant difference between oral and intravenous administration. However, data set forth in detail below, suggests that the absorption rate constant (Ka) is significantly increased when caffeine is administered through chewing gum. This means that the caffeine is moving into the systemic circulation at a significantly faster rate. A similar change in the onset of dynamic response has also been noted, e.g., alertness and performance.

It has additionally been surprisingly found that for at least certain agents that placing the agent in the chewing gum can have a triggering effect on the agent that may be in the systemic circulation. For example, it has been found that with respect to caffeine that is ingested orally, that after the ingestion of a certain amount of caffeine, and the elapse of a certain period of time, that further ingestion of caffeine has a

negligible effect on the individual. However, upon chewing gum with caffeine there has been observed a triggering effect that appears to create a synergistic effect with the caffeine that is in the systemic circulation. It is believed that this triggering effect will also be present with other agents, e.g., analgesics.

It is envisioned, that a variety of different medicaments and agents can be placed in the coating. For example, such agents include, *inter alia*, stimulants such as caffeine. Generally, such medicaments include, inter alia, analgesics, antibiotics, antivirals, antihistamines, anti-inflammatories, decongestants, antacids, muscle relaxants, psychotherapeutic agents, insulin, and cardiovascular agents. It is envisioned, that depending on the medicament, the resultant chewing gum can be used to treat, inter alia: coughs; colds; motion sickness; allergies; fevers; pain; inflammation; sore throats; cold sores; sinus problems; diarrhea; diabetics; depression; anxiety; and other maladies and symptoms. Specific agents/medicaments include, by way of example and not limitation: caffeine; aspirin; acetaminophen; ibuprofen; hydroxycitric acid; chromium picolinate; phosphatidylserine; nicotine; insulin; Echinacea purpurea; zinc; vitamin C; ginseng; kola nut; kaua kaua; and chamomile.

Preferably, the agents or medicaments are contained in the coating of the chewing gum formulation at levels of approximately 50 micrograms to 500 milligrams. The specific levels will depend on the active ingredient. For example, if chromium picolinate is the active ingredient in an embodiment, it would be present at a level of 50 micrograms per serving (2.8 grams of coated chewing gum); aspirin would be preset at a level of 325 milligrams per 2.8/gram serving. The level of medicament or agent in the coating of the chewing gum formulation is selected so as to create, when the gum is chewed, a sufficiently high concentration of the medicament or agent in the saliva.

For example, when the agent is a stimulant such as nicotine or caffeine, the level of the stimulant in the coating of the chewing gum should be such that it creates a saliva content of stimulant of approximately 15 to 440 ppm when the chewing gum is chewed for 2 minutes. At this level, a sufficient amount of stimulant will be delivered to the chewer to create the effects set forth in the application. If a medicament is used such as a medicinal (e.g., analgesics), sufficient medicinal should be present in the coating of the chewing gum to create a salvia content of approximately 1700 to approximately 4400 ppm after the chewing gum has been chewed for 2 minutes. For a botanicals (e.g., chamomile, kava, kola, nut, ginseng, and Echinacea), the agent should

be present in a sufficient amount to create a saliva content of approximately 85 to 1100 ppm when the chewing gum is chewed for 2 minutes. For a metabolizer, for example, chromium picolineate and hydroxi-chitic acid, the agents should be present in an amount to create a saliva content of approximately 0.5 to about 900 ppm when chewed for at least two minutes. If the agent is a vitamin or mineral (e.g., phosphatidy serine, vitamin C, and zinc), the agent should be present in the amount to create a saliva content of the vitamin or mineral of approximately 10 to about 250 ppm when chewed for 2 minutes.

Pursuant to the present invention, depending on the agent or medicament, the dosing regiment will change. For example, if the medicament is an analgesic, the chewing gum would be taken on an as needed basis. Of course, similar to the oral administration of an analgesic, there would be restrictions on the number of pieces of chewing gum, chewed, for example, not more often than one stick every four hours and not more often than four to five times a day.

If the agent is a stimulant such as caffeine to be used to enhance performance than the chewing gum would be chewed, in a preferred embodiment ten minutes or less before the performance. As set forth below in the experiment, it has been surprisingly found that for a chewing gum stick including caffeine, with another 5 minutes of chewing a high level of alertness is achieved.

A variety of methods can be used for constructing the coating of the chewing gum. Typically coatings are applied to chewing gum in a three-phase operation. In this regard, the first phase is to add a crude coating of an alternate application of syrup and powder is applied. This is followed by a second phase called the finishing coating in which finer powder and longer tumbling is used to produce a smooth finish. Finally a shellacking and polishing third phase is performed to provide a high-sheen smooth finish. In a preferred embodiment, the second phase is not used and the third phase is optional. As noted above, in contrast to typical coated chewing gum products, the products of the present invention include at least 50% to 75% by weight coating. Using only the first phase of the method, this large percent of coating can be applied to the product in a realistic time-frame.

In an embodiment, the coating comprises approximately 10 to about 30 % by weight syrup and approximately 70% to about 90 % by weight powder. For example, in a preferred embodiment, the coating comprises 20% syrup and 80% powder.

In an embodiment of constructing the coated chewing gum, first the syrup is distributed on the gum center. Then a portion of the powder is sprinkled on top to dry up the syrup. A further amount of syrup is added and powder supplied. This process is continued until the necessary amount of syrup and powder have been applied to the exterior of the chewing gum, e.g., 10 to 20 coating layers or more are applied. The coating which plays an important role as the masking agent, can include a combination of sugar, corn syrups, or in the case of a sugar-free product, various combinations of sugar alcohols, monomers, and polymers.

It has been found that by using this type of gross up coating process that advantages are achieved for the product containing medicament of the present invention. This is true whether or not the medicament is contained in the powder or in the syrup. Accordingly, if desired, the medicament can be contained in the syrup rather than in the powder.

Pursuant to the present invention, the coated product may not include a shellac or other finishing or shiny layer. It has been found, that the coating can comprise merely a matte finish and still function, not only satisfactorily, but has some advantages. In this regard, typically coated products that retain moisture on the coating along with a shellac layer may degrade due to moisture in the coating and therefore do not have an extended shelf-life. This is especially true with the thick coatings of the present invention. Such thick coatings absorb more moisture than thinner coatings. If a matte finish is utilized, although the thick coating layer can absorb the moisture, the matte finish allows the moisture to move into and out of the coating layer. This thereby prevents degradation of the product. Thus, the present invention provides a product having a thick coating with increased shelf-life.

The matte finish additionally not only allows a thick coating to be used but also ingredients that have high moisture absorption. Due to the matte finish, high moisture absorbing medicaments can be used without undue product degradation.

In an embodiment of the coating, dextrose or sucrose or combinations thereof function as the main ingredient. In a preferred embodiment, dextrose is utilized and the dextrose comprises approximately 50 to about 90% of the coating. The active ingredients or medicaments, in the coating may comprise as much as 30% of the coating down to very small amounts as long as the medication is efficacious. In a preferred embodiment, the flavors are powdered flavors and can range from 0.1% to

approximately 5%. High-intensity sweeteners such as aspartame, sucralose, and acesulfame-k can also be used in the coating and range from approximately 0.5 to about 5% of the coating. As noted above, these high-intensity sweeteners are excellent masking agents.

The coating including medicament or agent can surround a variety of different gum center compositions. Referring now to the chewing gum center, pursuant to the present invention, the gum center may be based on a variety of different chewing gums that are known. For example, the gum center can be low or high moisture, sugar or sugarless, wax containing or wax free, low calorie (via high base or low calorie bulking agents), and/or may contain dental agents.

Chewing gum generally consists of a water insoluble gum base, a water soluble portion, and flavor. The water soluble portion dissipates with a portion of the flavor of the gum over a period of time during chewing. The gum base portion is retained in the mouth throughout the chew.

The insoluble gum base generally comprises elastomers, resins, fats and oils, softeners and inorganic fillers. The gum base may or may not include wax. Typically, gum base comprises approximately 20 to about 40% of the gum product. However, because in the present invention such a high level of coating is used, the gum center is unusually small; otherwise the entire coating chewing gum piece would be too large for consumption. If a typical amount of gum base was used in the small gum center, it would result in an inadequate cud to masticate. Consequently, in the present invention, the base level is higher than normal. The insoluble gum base can constitute approximately 30% to about 90% by weight of the chewing gum, in an embodiment, the gum base comprises at least 50% of the chewing gum.

In an embodiment, the chewing gum base of the present invention contains about 20% to about 60% by weight synthetic elastomer, about 0% to about 30% by weight natural elastomer, about 5% to about 55% by weight elastomer plasticizer, about 4% to about 35% by weight filler, about 5% to about 35% by weight softener, and optional minor amounts (about 1% or less by weight) of miscellaneous ingredients such as colorants, antioxidants, etc.

Synthetic elastomers may include, but are not limited to, polyisobutylene with GPC weight average molecular weight of about 10,000 to about 95,000, isobutylene-isoprene copolymer (butyl elastomer), styrene-butadiene, copolymers having styrene-

butadiene ratios of about 1:3 to about 3:1, polyvinyl acetate having GPC weight average molecular weight of about 2,000 to about 90,000, polyisoprene, polyethylene, vinyl acetate - vinyl laurate copolymer having vinyl laurate content of about 5% to about 50% by weight of the copolymer, and combinations thereof.

Preferred ranges for polyisobutylene are 50,000 to 80,000 GPC weight average molecular weight and for styrene-butadiene are 1:1 to 1:3 bound styrene-butadiene, for polyvinyl acetate are 10,000 to 65,000 GBC weight average molecular weight with the higher molecular weight polyvinyl acetates typically used in bubble gum base, and for vinyl acetate-vinyl laurate, vinyl laurate content of 10-45%.

Natural elastomers may include natural rubber such as smoked or liquid latex and guayule as well as natural gums such as jelutong, lechi caspi, perillo, sorva, massaranduba balata, massaranduba chocolate, nispero, rosindinha, chicle, gutta hang kang, and combinations thereof. The preferred synthetic elastomer and natural elastomer concentrations vary depending on whether the chewing gum in which the base is used is adhesive or conventional, bubble gum or regular gum, as discussed below. Preferred natural elastomers include jelutong, chicle, sorva and massaranduba balata.

Elastomer plasticizers may include, but are not limited to, natural rosin esters such as glycerol esters or partially hydrogenated rosin, glycerol esters of polymerized rosin, glycerol esters of partially dimerized rosin, glycerol esters of rosin, pentaerythritol esters of partially hydrogenated rosin, methyl and partially hydrogenated methyl esters of rosin, pentaerythritol esters of rosin; synthetics such as terpene resins derived from alpha-pinene, beta-pinene, and/or d-limonene; and any suitable combinations of the foregoing. The preferred elastomer plasticizers will also vary depending on the specific application, and on the type of elastomer which is used.

Fillers/texturizers may include magnesium and calcium carbonate, ground limestone, silicate types such as magnesium and aluminum silicate, clay, alumina, talc, titanium oxide, mono-, di- and tri-calcium phosphate, cellulose polymers, such as wood, and combinations thereof.

Softeners/emulsifiers may include tallow, hydrogenated tallow, hydrogenated and partially hydrogenated vegetable oils, cocoa butter, glycerol monostearate, glycerol triacetate, lecithin, mono-, di- and triglycerides, acetylated monoglycerides, fatty acids (e.g. stearic, palmitic, oleic and linoleic acids), and combinations thereof.

Colorants and whiteners may include FD&C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide, and combinations thereof.

The base may or may not include wax. An example of a wax-free gum base is disclosed in U.S. Patent No. 5,286,500, the disclosure of which is incorporated herein by reference.

In addition to a water insoluble gum base portion, a typical chewing gum composition includes a water soluble bulk portion and one or more flavoring agents. The water soluble portion can include bulk sweeteners, high-intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, acidulants, fillers, antioxidants, and other components that provide desired attributes.

Softeners are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. The softeners, which are also known as plasticizers and plasticizing agents, generally constitute between approximately 0.5% to about 15% by weight of the chewing gum. The softeners may include glycerin, lecithin, and combinations thereof. Aqueous sweetener solutions such as those containing sorbitol, hydrogenated starch hydrolysates, corn syrup and combinations thereof, may also be used as softeners and binding agents in chewing gum.

Bulk sweeteners include both sugar and sugarless components. Bulk sweeteners typically constitute about 5% to about 95% by weight of the chewing gum, more typically, about 20% to about 80% by weight, and more commonly, about 30% to about 60% by weight of the gum. Sugar sweeteners generally include saccharide-containing components commonly known in the chewing gum art, including but not limited to, sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, levulose, glactose, corn syrup solids, and the like, alone or in combination. Sugarless sweeteners include, but are not limited to, sugar alcohols such as sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates, maltitol, and the like, alone or in combination.

High-intensity artificial sweeteners can also be used, alone or in combination, with the above. Preferred sweeteners include, but are not limited to, sucralose, aspartame, salts of acesulfame, altitame, saccharin and its salts, cyclamic acid and its salts, glycerrhizinate, dihydrochalcones, thaumatin, monellin, and the like, alone or in combination. In order to provide longer lasting sweetness and flavor perception, it may be desirable to encapsulate or otherwise control the release of at least a portion of the artificial sweetener. Such techniques as wet granulation, wax granulation, spray

drying, spray chilling, fluid bed coating, coacervation, and fiber extension may be used to achieve the desired release characteristics.

Combinations of sugar and/or sugarless sweeteners may be used in chewing gum. Additionally, the softener may also provide additional sweetness such as with aqueous sugar or alditol solutions.

If a low calorie gum is desired, a low caloric bulking agent can be used. Examples of low caloric bulking agents include: polydextrose; Raftilose, Raftilin; Fructooligosaccharides (NutraFlora); Palatinose oligosaccharide; Guar Gum Hydrolysate (Sun Fiber); or indigestible dextrin (Fibersol). However, other low calorie bulking agents can be used.

A variety of flavoring agents can also be used, if desired. The flavor can be used in amounts of about 0.1 to about 15 weight percent of the gum, and preferably, about 0.2% to about 5% by weight. Flavoring agents may include essential oils, synthetic flavors or mixtures thereof including, but not limited to, oils derived from plants and fruits such as citrus oils, fruit essences, peppermint oil, spearmint oil, other mint oils, clove oil, oil of wintergreen, anise and the like. Artificial flavoring agents and components may also be used. Natural and artificial flavoring agents may be combined in any sensorially acceptable fashion.

The gum center can be prepared using a variety of different methods and machinery known in the art. For example, the formulation can be mixed using a sigma blade mixer. The center formulation may also be made by continuous processing equipment known in the art. Conventional sheeting and scoring machinery can be used to form and score the centers or the centers can be made on a forming machine that involves a drop frame and nitrogen cooling allowing spheres, ovals, and other shapes to be made.

By way of example, and not limitation, examples of some coated chewing gum formulations including a medicament or agent are as follows:

ACETAMINOPHEN COATED BUBBLE GUM

Gum Center (1 gram)

Ingredient	Grams
Gum Base	400.0
Corn Syrup	91.0
Glycerine	49.0
Sugar	829.9
Red Dye	0.7

Aspartame	14.0
Bubble Gum Flavor	15.4
	1400.0

Coating (1 gram)

Ingredient	Grams
Acetaminophen	80.0
Encapsulated Aspartame	20.0
Aspartame	50.0
Salt Flour	2.5
Dextrose	643.5
Bubble Gum Flavor	4.0
	800.0

ACETAMINOPHEN COATED CHEWING GUM

Gum Center (1 gram)

Ingredient	Grams
Xylitol	56.0
Natural Peppermint Flavor	27.0
Natural Peppermint Flavor	25.0
Natural Menthol	9.0
Natural Peppermint Flavor	26.0
Glycerine 96% USP	14.0
Bubble Gum	480.0
Firm Modifier	90.0
Aspartame	6.0
Ace-K	9.0
Gum Base	620.0
Corn Syrup	112.0
Powdered Sugar	406.0
	1400.0

Coating (2 grams)

Ingredient	Grams
Acetaminophen	335.0
Natural Peppermint	7.0
S.D. Menthol	6.0
Dextrose	1,221.0
Aspartame	32.0
	1,601.0

PSEUDOEPHEDRIN COATED GUM

Gum Center (1 gram)

Ingredient	Grams
Xylitol	56.0
Natural Peppermint Flavor	27.0
Natural Peppermint Flavor	25.0
Natural Menthol	9.0
Natural Peppermint Flavor	26.0
Glycerine 96% USP	14.0
Gum Base	670.0
Firm Modifier	90.0
Aspartame	6.0
Ace-K	9.0
Gum Base	140.0
Corn Syrup	112.0
Powdered Sugar	406.0
	1,400.0

Coating (2 grams)

Ingredient	Grams
Dextrose	1,476.00
Eucalyptus*	2.00
Menthol*	30.00
Aspartame	32.00
Pseudoephedrin	60.00
	1,600.00

* sprayed dried

PEPPERMINT CAFFEINE COATED CHEWING GUM

Gum Center (1 gram)

Ingredient	Grams
Xylitol	56.0
Natural Peppermint Flavor	27.0
Natural Peppermint Flavor	25.0
Natural Menthol	9.0
Natural Peppermint Flavor	26.0
Glycerine 96% USP	14.0
Gum Base	620.0
Firm Modifier	90.0
Aspartame	6.0
Ace-K	9.0
Gum Base	140.0
Corn Syrup	112.0
Powdered Sugar	406.0
	1,400.0

Coating (2 grams)

Ingredient	Grams
Caffeine	100.0
Peppermint	13.0
Dextrose	1,455.0
Aspartame	32.0
	1,600.0

By way of example, and not limitation, experiments and examples testing chewing gum including a medicament or agent in the gum body or coating are as follows:

Experiment No. 1

Single dose, placebo controlled, randomized, two-way crossover study in 20 subjects to evaluate the effect of 50 mg caffeine gum compared to placebo gum-on positive and negative mood affects. Healthy subjects 18-65. Screening questionnaire to evaluate average caffeine consumption, tobacco drug and alcohol status. Any subjects taking medications with a CNS affect were excluded from the study. Approximately 2 hours on two occasions separated by at least 24 hours.

Dosing: 1 x stick of caffeine gum to be chewed for 30 minutes. The chewing gum had the formulation set forth above in the table entitled caffeine gum.

The subjects were instructed that they were to have caffeine, alcohol or other drug use for at least 8 hours prior to test. No tobacco products for at least 2 hours prior to test. Subjects must have been awake and active for at least 8 but no more than 16 hours prior to starting the test. Subjects will be required to complete a 10 part questionnaire at the following time points (-20, -10, -5 and at 2, 5, 10, 15, 20, 30, 40 and 1 hour after starting to chew the gum. Appropriate analysis of comparison of each individual item of the test and grouped analysis for both positive and negative affect.

Data was corrected for baseline data (-5 minute reading) at each time point. Means and standard deviations for both active and placebo groups were evaluated for all time points.

The results of the analysis are set forth in Figure 2. Figure 2 graphically illustrates alertness versus time. These results demonstrate that by 5 minutes the subject reported that they were quite a bit alert. The alertness response was based on reference Panas feeling and emotion scale.

Experiment No. 2

A randomized, single-dose, two-way crossover study was conducted with six (6) healthy, adult, non-tobacco-using male subjects. A single 100 mg does of caffeine was administered in each study period after an overnight fast. The test treatment was two 50mg caffeine chewing gum pieces (sticks), which were chewed for 15 minutes and removed. The reference treatment was one 100mg chewable No-Doz® tablet, which was chewed and swallowed. One of the treatments was given in each period; the order of administration was according to the dosing randomization schedule. There was a 7-day washout between treatments.

Blood samples were collected pre-dose and over 15 hours after each dose. Plasma concentrations of caffeine were measured by a fully validated chromatographic procedure. Samples from subject with measurable pre-dose levels of caffeine were corrected for these levels. Pharmacokinetic parameters were calculated from the adjusted data and statistical analyses were performed to compare the test and reference treatments.

Clinical Procedures

A. Subject Selection.

The 6 subjects who participated in this study were healthy males, in the age range of 25 to 35 years, and within 15% of their ideal weight as specified in the protocol.

All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination, and clinical laboratory evaluations. Any laboratory value or vital sign measurement more than 10% outside the normal range was evaluated individually by the investigator. All were determined

to be not clinically significant for those subjects enrolled in the study. All screening evaluations were performed within 28 days of initial dosing.

B. Drug Supplies.

Formulations:

Test (A) - Two 50mg chewing gum sticks, Amurol Confections Co. (Lot #ALRT7/9/19/96, No exp. Date)

Reference (B) - One 100mg No-Doz® chewable table, Bristo-Myers Products (Lot #601041, Exp. date 10/98).

Administration: The subjects received the test and reference after an overnight fast. The subjects randomized to the test first drank 240 ml of room temperature tap water. The chewing gum pieces were then chewed for 15 minutes and deposited into a labeled vial. The subjects randomized to the reference chewed the No-Doz® tablets and then drank 240 ml of room temperature tap water. The order of treatment administration was according to the randomization schedule.

All doses were administered at one-minute intervals beginning at 0700 hours. A thorough mouth check was performed to ensure that the chewable tablet was swallowed. A schedule of the actual dosing times, dates and treatment assignments is included in Table C2. All subjects remained under observation sitting upright or standing for at least two hours after each dosing. Six subjects were dosed in both Period I and Period II.

C. Study Conduct.

Confinement, Meals: During the confinement periods of this study, the subjects were housed and fed at the clinical facility.

In each period, the subjects reported for check-in (Day -1) at least 12 hours before dosing. Meals were provided on check-in day and completed at least 10 hours prior to scheduled dosing time. No food or beverages (except water) were permitted after 2100 hours on Day -1.

During confinement (Day 1), standardized, caffeine-free meals or snacks were served at 4, 10 and 14 hours after dosing, as specified on the Activity Schedule and Menu found in Section 3. The same menu was used during each study period. The subjects consumed at least 95% all food and beverages that were required. The subjects were released from the clinical facility approximately 2200 hours after dosing in each study period. A 7-day washout separated the dosings.

Restrictions: Prior to check-in for the study, the subjects were instructed to take no prescribed medications for at least 14 days prior to the initial dosing and throughout the study. No over-the-counter medications were permitted for 72 hours before dosing in each study period. No medications were permitted during confinement except those administered. Subjects were also instructed to abstain from any products containing alcohol or caffeine for 48 hours prior to dosing and throughout each confinement. None of the subjects reported taking any restricted substance within the time frame indicated.

During the confinement periods of the study, water was restricted from one hour before until one hour after dosing except for water (240 ml) administered with the dose. Water was permitted ad lib at all other times. Subjects remained sitting upright or standing for 2 hours after each dosing, except as required for study procedures. No strenuous physical exercise was permitted during confinement.

Safety: Urine drug screens were performed at each check-in to test for alcohol, marijuana and cocaine metabolites.

Blood pressure (sitting), pulse rate, respiratory rate and oral temperature were measured before each dosing. The investigator considered the measurements of all subjects as clinically acceptable for dosing.

Blood pressure and pulse rate measurements (sitting) were obtained approximately one hour after each dose and prior to release in each study period to monitor the health of the subjects. Measurements were repeated if clinically warranted.

A blood sample was collected at the time of the last sample of the study for a hematocrit determination. All hematocrit values were within 10% of the normal range (41-50%).

Adverse Events: The subjects were monitored throughout the study for any adverse experiences. They were encouraged to report signs, symptoms, and any changes in health to the study nurse. None of the subject reported any adverse events during this study.

Pharmacokinetic Samples: In each period, blood samples were collected prior to dosing and at the following nominal times after dosing: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 15 hours. The samples were labeled at the time of collection with a unique 6-digit code number. Pre-dose samples were collected within 30 minutes before

dosing. All plasma samples were stored frozen between -18_C and -20_C until transfer to the laboratory for analysis, with the exception of one day.

Subject Completion: A total of 6 subjects were entered into the study and all subjects completed one study.

Analytical Procedures

A. Quality Control.

Standards and Controls: Calibration standards were prepared spiking a pool of human, interference-free, heparinized plasma with caffeine (USP Reference, Lot I). The plasma was obtained from Interstate Blood Bank (Memphis, TN). The standards were prepared to contain 0.050, 0.100, 0.200, 0.500, 1.00, 2.00 and 5.00 g/ml of caffeine.

The caffeine standards and controls were divided into 2.5ml aliquots and stored in the laboratory in polypropylene snap-cap tubes frozen to at least -19 C.

The pre-study within-run coefficient of variation ranged from 0.915% to 2.54%. The relative accuracy of the procedure was estimated, through comparison of the measured concentration means of the control samples against their theoretical concentrations, and was found to average 99.5% for caffeine.

Run Acceptance Criteria: Chromatographic peak responses and peak response ratios were monitored using an electronic integrator. Each chromatographic tracing was inspected for acceptable retention times, peak shapes, resolution and integration before the peak response ratios (analyte-to-internal standard) were entered into the computer.

The acceptable limit of quantization for the run was evaluated through comparison of the mean response of the lowest concentration standards (0.050 _g/ml) with the responses of any interferences observed in the water blank, matrix blank and zero standard. The limit of quantization for the run was defined as the concentration at which the signal-to-noise ratio was at least 2.

Samples, standards and controls with an internal standard peak response which deviated more than ±25% from the mean within-run peak response of the internal standard (calculated for all standards and controls) were rejected.

The response ratio for each remaining non-zero standard was plotted as a function of concentration. A linear regression was calculated (R/S 1, version 4.3) by the method of least-squares using $(1/CONC)^2$ as a weighting factor. With this

calibration line, a calculated concentration was determined for each standard sample. Any standard differing by more than ±25% from its theoretical value was excluded from the regression and the regression was recalculated. The analyte concentrations in the samples and the controls were estimated from the calibration line by use of the equation: (RATIO - INTERCEPT)/SLOPE.

The analytical run was considered acceptable if 4 of 6 controls passed established acceptance criteria and that at least one control sample was acceptable within each concentration range. Controls within an analytical run were considered acceptable if the low control values differed by no more than ±20% and the middle and high controls differed by no more than ±15% from their theoretical values. The concentrations o the controls were graphically displayed to permit visual confirmation of acceptability and identification of trends.

B. Sample Analysis.

Sample Storage and Stability: The plasma samples, which were collected in the clinic were transferred to the laboratory and stored frozen to at least -19 C until analyzed. Samples were not identified to the analysts by treatment group. All subjects' samples were analyzed within 19 days of the initial sampling. The frozen stability of caffeine in plasma has been confirmed for 138 days.

Peak Identification: The retention times of the analyte and the internal standard were identified, in any given analytical run, by comparison to stock standards chromatographed at the beginning of the run and to processed standards chromatographed through the run.

Pharmacokinetic and Statistical Procedures

A. Pharmacokinetic Data.

All the available data from 6 subjects with reported caffeine concentrations were used in the pharmacokinetic analyses. Several subjects had pre-dose samples which contained measurable concentrations of caffeine. For each of these subject's data, the measured concentration at each sampling time was corrected by subtracting the level of caffeine at that time predicted from the decay of the pre-dose level. The decay curve was constructed using the elimination rate observed in the same period as the decay constant. After adjustment, each pre-dose level was 0.0 g/ml, and each post-dose concentration was reduced accordingly.

Pharmacokinetic parameters (areas, times to peak, and elimination rates and half-lives) were calculated using the actual rather than the scheduled time of sample collection. Graphical presentations of individual subject results also used the exact times of sample collection. Graphical presentations of mean results used the scheduled times of sample collection.

Peak concentration (Cmax) was the observed maximum value (corrected for pre-dose levels, if necessary) during the collection period of 0 to 15 hours. The time to peak concentration (Tmax) was the time at which Cmax was observed (or first observed, if more than one peak was present).

The apparent first-order elimination rate (Ke) was estimated as the absolute value of the slope of the regression line for the terminal log-linear concentration-time values. The values included in the regression analyses were determined by examination of the individual subject plots of natural logarithm of concentration against time. Elimination half-life (t-½) was calculated as 0.693/Ke.

Area under the curve (AUC) to the time of the last non-zero concentration (C_t) was calculated by the linear trapezoidal method. Area to infinite time (AUCinf) was calculated by extrapolating AUC by the addition of the quantity: C_t/Ke.

B. Statistical Analyses.

Statistical analyses were performed using the General Linear Models (GLM) procedures of the SAS statistical program. Hypothesis testing for treatment effects was conducted at =0.05. The statistical model contained main effects of sequence, subject within sequence, period, and treatment. Sequence effects were tested against the type III mean square term for subjects within sequence. All other main effects were tested against the mean square error term.

The observed and calculated pharmacokinetic parameters as well as the caffeine concentrations at each of the individual collection times were compared statistically.

Power for the pair-wise pharmacokinetic comparisons was calculated as the probability (=0.05) of detecting a difference equal to 20% of the mean for the reference treatment in the comparison, or a ratio of 1.25 for In-transformed results. [Winer, BJ. *Statistical Principles In Experimental Design.* NEW YORK: McGraw-Hill Book Company (1962) 21-26.]

Confidence Intervals (90%) for pair-wise area and peak concentrations comparisons were calculated by the t-test approach (2,1-sided) at =0.05 each side.

The intervals were computed for the "true" mean test-to-reference treatment ratio (or geometric mean ratio for In-transformed results).

Discussion and Results

Statistical analyses were performed on the caffeine data in order to compare the test chewing gum to the chewable reference tables. Natural log-transformation of the area and Cmax parameters was also performed and analyzed statistically. Table 1, which follows, summarizes the results (n=6) of the statistical analyses of the major bioavailability parameters.

Statistical comparisons of the test and reference formulations at each sampling time are summarized in Table 2.

Conclusion

The caffeine chewing gum pieces appear to have a much faster rate of absorption that the No-Doz® chewable tablets. The areas and peak concentrations of the chewing gum were less than half that of No-Doz® even though the gum base released one-half the caffeine that the tablet did. And the time to reach a peak for the gum was 30 minutes earlier than for the tablet.

Table 1: Comparisons of caffeine results for 50mg chewing gum pieces (Test) vs. 100mg No-Doz® chewable tablets (Reference) administered as a single 100mg dose under fasting conditions to 6 subjects.

Parameter	Least Squares Means[1]		Test/Ref. Ratio[2]	Power[3]	90% Confidence Interval[4]	
	Test	Reference			Lower	Upper
AUC 0-t (g-hr/ml)	7.26	17.65	0.412*	0.50	0.246	0.577
AUCinf (g-hr/ml)	9.60	23.72	0.405*	0.39	0.211	0.598
Cmax (g/ml)	0.92	2.15	0.429*	0.76	0.309	0.548
Tmax (hour)	1.08	1.58	0.684	0.22	–	–
Ke (1/hour)	0.1241	0.1058	1.173*	0.86	–	–
Elimhalf (hour)	5.97	6.97	0.857*	0.86	–	–
Ln-Transformed Data						
AUC 0-t (g-hr/ml)	6.22	17.44	0.357*	0.15	0.239	0.532
AUCinf (g-hr/ml)	7.66	23.00	0.333*	0.13	0.212	0.524
Cmax (g/ml)	0.84	2.14	0.391*	0.17	0.272	0.562

1 Least squares geometric means for In-transformed data.

2 Test/Ref Ratio calculated as Test mean divided by Reference mean.

3 Power to detect a difference of 20% (original data) or a ratio of 1.25 (In-transformed data).

4 Confidence interval on the ratio.

* Detected as statistically significant by ANOVA (=0.05).

Table 2: Summary of caffeine statistical comparisons at each sampling time comparing 50mg chewing gum pieces (Test) vs. 100mg No-Doz® chewable tablets (Reference) administered as a single 100mg dose under fasting conditions to 6 subjects.

Sample Time	Collection (Hour)	Least Squares Means (_g/ml)		Significance *
		Test	Reference	
1	Pre-dose	0.00	0.00	
2	0.25	0.23	0.36	0.0269
3	0.50	0.79	1.18	None
4	1.00	0.83	1.91	0.0008
5	1.50	0.84	2.05	0.0006
6	2.00	0.75	2.01	0.0004
7	2.50	0.72	1.92	0.0001
8	3.00	0.68	1.78	0.0006
9	4.00	0.66	1.64	0.0006
10	6.00	0.57	1.33	0.0046
11	8.00	0.47	1.10	0.0088
12	10.00	0.37	0.90	0.0052
13	12.00	0.28	0.75	0.0021
14	15.00	0.22	0.56	0.0068

* Statistical comparisons to test for the equivalence of treatment effects were performed at an a level of 0.05. The actual p-value is indicated at the time where statistically significant differences ($p<0.05$) were detected; "None" indicates that no significance was detected ($p<0.05$) at that time.

Figure 3 illustrates graphically least squares mean plasma concentration (~=6). Concentration of caffeine in (reg/ml) versus hours of the dose is illustrated graphically; chewing gum provided 50mg of caffeine versus 100mg of No-Doz® tablet. It should be noted that although in Figure 2 the blood concentration level of caffeine is approximately 50% that of No-Doz®, the amount of caffeine delivered by the chewing gum was 50% that of the No-Doz®.

Experiment No. 3

The following protocol was followed. The chewing gum formula set forth on page 15 under the heading caffeine gum was used. Subjects chewed gum for 5 minutes. Then, the gum cuds were then collected and analyzed for caffeine. At T-10 minutes, the gum was collected after chewing for 10 minutes and then had the caffeine analyzed. This was repeated for all the time figures up to time 60 minutes. "Times 0" refers to non-chewed gum product. All these T-0 to T-60 minute gum samples were from the same lot of chewing gum.

The results are as follows:

Table 3

Timed Chewed Minutes	Mg Caffeine remaining in gum	Actual % Caffeine remaining in gum	Relative % Caffeine remaining in gum
T_0	57.96	2.07	100.00
T_5	16.80	0.60	28.70
T_{10}	7.56	0.27	12.98
T_{20}	1.68	0.06	3.01
T_{30}	0.84	0.03	1.32
T_{40}	0.00	0.00	0.00
T_{60}	0.00	0.00	0.00

Figure 3 illustrates graphically % caffeine remaining over chew-out time in minutes.

Experiment No. 4

To detect adsorption in the oral cavity, the following experiment was carried out. Samples of Stay-Alert Cinnamon flavored caffeine gum (Lot 713176) were analyzed for caffeine and found to contain 53.44±0.52 mg per stick. Two subject (S1 and S2) were recruited to chew the gum. Each subject chewed one stick of gum for 20 minutes, expectorating all saliva into a container. After chewing, each rinsed twice with 10 ml of water (20 ml total) and added the rinse water to the collected saliva. The volume of this solution was brought up to 75 ml with distilled water. S2 repeated the extraction process with a new stick of gum.

The chewed gum cuds and the saliva solutions were analyzed for caffeine by gas chromatography. (A spiking study was also conducted which showed recovery of caffeine from gum cuds and saliva solutions to be 99.25% and 103.50% respectively. Measured caffeine levels were not corrected for these recoveries as they were not

deemed significantly different from 100%.) The results of the experiment are reported in Table 4.

Table 4			
	S1	S2a	S2b
Volume of Saliva (ml)	50	30	30
Initial caffeine level (mg)	53.44	53.44	53.44
Caffeine remaining in cud (mg)	2.00	13.09	15.12
Caffeine in Saliva (mg)	45.69	30.26	28.97
Total Caffeine recovered (mg)	47.69	43.35	44.09
Unrecovered caffeine (mg)	5.75	10.09	9.35
Percent of released unrecovered	11.2	25.0	24.4

It is believed that the unrecovered caffeine was adsorbed through mucous membranes in the oral cavity. Thus between 11 and 25% of the released caffeine was adsorbed orally. Note that the higher concentration of caffeine in saliva for S2 may have contributed to the higher adsorption in that subject.

Experiment No. 5

The following gum center formulation was made as a gum pellet center:

Gum Center	%
Gum Base	47.00
Sorbitol	39.52
Liquid Sorbitol	7.50
Flavors	2.36
Encapsulated Flavors	2.00
Glycerin	0.75
Encapsulated Sweeteners	0.87
	100.00

The gum pellet was coated with the following gum coating formulation:

Gum Coating	% of Syrup 1	% of Syrup 2
Xylitol	63.03	74.35
Water	11.14	13.15
40% Gum Tahla Solution	20.87	7.96
Titanium Dioxide Whitener	0.37	0.44

Peppermint Flavor[1]	0.81	0.00
Caffeine	3.78	4.10
	100.00	100.00

Initial center piece weight was 0.956 grams. Gum was coated to a finished piece weight of 1.46 grams to give a 34.5% coating. Coating syrup 1 was used to coat the first 60% of the coating to a piece weight of 1.26 grams. Coating syrup 2 was used to coat to the final piece weight. Individual piece analysis of 5 pieces yielded a level of 26.1 mg of caffeine per piece. For a 2 piece dosage, caffeine level is 52.2 mg.

This gum product was used in a caffeine absorption study to compare release and absorption uptake of caffeine from gum and beverages. The test results showed that gum is a faster delivery vehicle for caffeine when compared to the same level in beverages as measured by blood plasma caffeine. Caffeine was taken up faster in the test subject's plasma after delivery via gum than after delivery of same caffeine dose via coffee, cola, and tea.

Comparisons of caffeine delivery between chewing gum and the three beverages are demonstrated by statistically significant differences in one or more of the following parameters:

1. Plasma caffeine concentration is significantly greater for gum vs. beverages within the first 10 to 30 minutes after caffeine delivery. This correlates to faster uptake.

2. Plasma absorption rate constant (A-rate) larger for gum vs. one or more beverages (2). Plasma absorption half life (abs. half-life) smaller for gum vs. one or more beverages (2). Time of peak caffeine plasma.

A clinical trial study was performed where six subjects participated in the test, blood was drawn and plasma separated. Blood sampling occurred prior to, and at present time intervals following a caffeine level of 50-55 mg released through the test delivery vehicle. Five different studies were completed: gum (with saliva swallowed, G2), gum (with saliva expectorated, G3), coffee (ingested COF), cola (ingested COK), and tea (ingested T). Blood samples of 5 ml were collected and the plasma portion separated, stored, and extracted and analyzed. A method was developed for the

1 Flavor added in 2 additions after 10th and 15th within coating syrup 1.

extraction and analysis of caffeine in fluids, which reports results as the concentration of caffeine in the plasma.

Data from the six subjects participating in the study were compiled, analyzed, and graphed, with mean plasma caffeine concentrations at specific time intervals determined. Analysis of variance (ANOVA) were performed on the means to determine statistical significance.

Phamacokinetic parameters were determined through Wagner's 1967 Method of Residuals using a pharmacokinetic software package. Absorption rate constants and absorption half-life were also determined through the analysis of the absorption phase of the plots by linear regression since the absorption phase followed zero order kinetics.

The conclusions were as follows:

1. There was a faster uptake of caffeine in plasma during the early time intervals post dose 10 minutes to 25 minutes (T10-T25) via gum delivery vs. the same level of caffeine delivered via coffee and cola. For example, the average level of plasma caffeine (at T=10 minutes) present after gum chew is 0.545 g/ml compared to 0.186 g/ml for coffee and 0.236 g/ml for cola. In other words, with the same level of caffeine being delivered from the three different vehicles, at T10 there is 3 times more caffeine present in plasma after chewing gum than from ingesting coffee and 2 times more caffeine from gum than from cola. The results of the tea study proved to be too variable due to instrument problems and repeat freeze/thawing of the samples. They were not included in the calculations.

2. Classical pharmacokinetic parameters, T-max, A-rate constant, abs. half-life, do not tell the story of faster uptake in the time interval of interest (T10-T25) in this study. This is due in part to the calculation using the Method of Residuals. This method was derived using classical pharmacokinetic curves which do not have much fluctuation in the data in that the drug concentration (usually measured every hour) increases to a sharp T-max, then decreases, without any fluctuation. In comparison, the data did contain minor fluctuations, due most likely to a combination of factors: measurement of plasma concentrations every five minutes rather than every quarter hour to one hours, caffeine binding with plasma protein, combination of both sublingual and gut absorption being detected. The plasma caffeine concentration followed the same trends as in classical pharmacokinetic curves, except that the

concentration increased to a broad T-max, then decreased, and some of the points in the curve fluctuated up and down.

A-rate constant and abs. half-life determinations were also made through linear regression. No significant differences were noted in the means, though a trend was noted: the A-rate for the gum study (G2) was greater than that for coffee and cola for subjects 1-4 and the abs. half-life for the G2 study was less than that for coffee and cola for subjects 1-4. For example, the G2 abs. half-life averaged 13 ± 4 minutes for subjects 1-4, 28 ± 2 minutes for subjects 5 and 6, indicating faster absorption between the subjects. The amount of caffeine absorbed sublingually was 21 ± 7 mg for subjects 1-4, and 10 ± 1 mg for subjects 5 and 6 accounting for the increased A-rate and decreased abs. half-life in subjects 1-4. An ANOVA separating subjects 1-4 from 5 and 6 indicated that for subjects 1-4 cola abs. half-life is statistically greater than G2 abs. half-life ($p=0.10$), and the G2 A-rate is statistically greater than both the cola and coffee A-rate ($p=0.05$).

3. It was shown that significant levels of caffeine are absorbed sublingually directly into the bloodstream via delivery from gum. This was demonstrated through the testing of caffeinated gum where the saliva was expectorated. Even though the saliva was expectorated, 20-50% of the caffeine was absorbed through the oral cavity. This accounts for the early uptake into the bloodstream.

Experiment No. 6

The following formulation was made:

Gum Center	%
Gum Base	33.00
Calcium Carbonate	13.00
Sorbitol	44.23
Glycerin	4.00
Flavors	2.32
Encapsulated Caffeine[2]	1.50
Free Caffeine	0.45
Lecithin	0.60
Encapsulated Sweeteners	0.90
	100.00

2 Spray dried maltodextrin/caffeine at 50% active caffeine.

Gum Coating	Coating Syrup 3. %	Coating Syrup 4. %
Xylitol	64.14	76.23
Water	11.14	13.15
40% Gum Tahla Solution	20.87	7.96
Titanium Dioxide Whitener	0.40	0.40
Peppermint Flavor[3]	1.40	0.00
Sweeteners	0.27	0.27
Carnauba Wax/ Talc Polishing Agents	0.00	0.27[4]
Caffeine	1.78	1.72
	100.00	100.00

Initial center piece weight was 0.995 grams. Gum was coated to a finished piece weight of 1.52 grams to give a 34.5% coating. Coating syrup 3 was used to coat the first 60% of the coating to a piece weight of 1.30 grams. Coating syrup 4 was used to coat to the final piece weight. Individual piece analysis of 5 pieces yielded a level of 20.0 ± 0.8 mg of caffeine per piece. For a two piece dosage, caffeine level is 40.0 mg.

This gum product was used in a caffeine absorption study to compare release and absorption uptake of caffeine from gum versus pills. The test results showed that gum is a faster delivery vehicle for caffeine when compared to a similar level in a pill as measured by blood plasma caffeine. Caffeine was taken up faster in the test subject's plasma after delivery via gum than after delivery of same caffeine dose via a pill.

Data from the six subjects participating in each study were compiled, analyzed, and graphed, with mean plasma caffeine concentrations at specific time intervals determined. Analysis of variance (ANOVA) and Student t-Tests were performed on the means to determine statistical significance. Pharmacokinetic parameters were done using a pharmacokinetic software package. The gums tested were pellet from Experiment No. 5, containing all the caffeine in the coating and delivering approximately 50 mg caffeine after chewing two pellets (designated as G2, G4, or 50 mg pellet), and Experiment No. 6, containing caffeine in the coating and center, and delivering approximately 40 mg caffeine after chewing two pellets (designated G5 or 40 mg pellet). Both pellets were compared to Pro-Plus™ 50 mg tablet is manufactured by the product license holder: PP Products, 40 Broadwater Road, Welayn Garden City,

[3] Flavor added in 3 additions after 3 separate syrup addition within coating syrup 1.

[4] Polished after completion of coating.

Harts, AL7 Bay, UK. Caffeine analysis were analyzed at 48.3 mg ± 1.4 mg caffeine per pill (avg. of n=5).

It was concluded that caffeine uptake in the bloodstream was faster for gum than a pill, based on the following:

1. Faster uptake of plasma caffeine via gum delivery was found during the early time intervals post dose 5 minutes to 50 minutes (T5-T50) when compared to the same level of caffeine delivered via a pill (50 mg). For example, with the same level of caffeine being delivered from the two different vehicles, on average, at T5 there is 30 times more caffeine detected in plasma after chewing gum (0.205 g/ml). Average plasma caffeine levels significantly greater than the pill at a=0.01 for T5, and a=0.005 for T10.

2. Classical pharmacokinetic parameters, T-Max (time for peak plasma caffeine concentration) and Abs. half-life (absorbence half-life, time for caffeine concentration to be half of peak) were significantly different for caffeine delivered via 50 mg pellet gum (Experiment No. 5) than via a 50 mg pill. Faster uptake of plasma caffeine was demonstrated via delivery from gum compared to a pill due to the average plasma Abs. half-life and average plasma T-Max being significantly smaller for gum than the pill. For the 50 mg pellet gum, the average Abs. half-life = 12.84 min. and the average T-Max = 36.5 min. compared to the 50 mg pill with an average Abs. half-life =24.47 min (pill significantly greater than gum, a = 0.0075), and an average T-Max = 73.67 min (pill significantly greater than gum, a = 0.0075), and an average T-Max = 73.67 min (pill significantly greater than gum, a = 0.005). In other words, after ingesting a pill, it takes a longer amount of time to reach half of the peak plasma caffeine concentration and the peak plasma caffeine concentration than after chewing gum delivering the same level of caffeine.

3. The Abs. Rate Const. (absorption rate constant, rate at which caffeine absorbs into the bloodstream) was significantly greater for 50 mg pellet gum (Experiment No. 5) than for the 50 mg pill, indicating that caffeine is absorbed at a greater rate after gum delivery than after delivery of the same dosage via a pill. For the 50 mg pellet gum, the average Abs. Rate Const. = 0.060 compared to the 50 mg pill with an average Abs. Rate const. = 0.031 (gum significantly greater than pill, a = 0.005).

4. The test also demonstrated faster uptake of plasma caffeine via the product of Experiment No. 6, 40 mg pellet gum, delivery during the early time intervals post dose 10 minutes to 30 minutes (T10-T30) when compared to 50 mg of caffeine delivered via a pill. Significance levels ranged from a= 0.05 to a= 0.20. For example, the average level of plasma caffeine (at T=10 minutes) present after 40 mg pellet gum is chewed is 0.228 _g/ml compared to 0.034 _g/ml for pill (difference was slightly significant, a=0.2). In other words, with caffeine being delivered from the two different vehicles at T10 there is 6.7 times more caffeine detected in plasma after chewing the product of Experiment No. 6 gum caffeine than after ingesting a pill, even though the pill delivered approximately 50 mg caffeine, and the product of Experiment No. 6 delivered approximately 40 mg. At T5, on average there was 13 times more caffeine detected in plasma after chewing Experiment No. 6 gum than after ingesting a pill.

5. Classical pharmacokinetic parameters, T-Max and Abs. half-life were significantly different for caffeine delivered via the product of Experiment No. 6 40 mg pellet gum than via a 50 mg pill. Faster uptake of plasma caffeine was demonstrated via delivery from the product of Experiment No. 6 gum compared to a pill due to the average plasma Abs. half-life and average plasma T-Max being significantly smaller for gum than the pill. For the 50 mg Experiment No. 5 gum, the average Abs. half-life = 18.33 min. and the average T-Max = 45 min compared to the 50 mg pill with an average Abs. half-life = 24.47 min (pill significantly greater than gum, a=0.05), and an average T-Max = 73.67 min (pill significantly greater than gum, a=0.15). Even though the product of Experiment No. 6 delivered 40 mg caffeine compared to delivery of 50 mg via a pill, it still took a longer amount of time to reach half of the peak plasma caffeine concentration for the pill than for the gum.

6. It was concluded that gums formulated with all the caffeine in the pellet coating delivered caffeine more quickly to the plasma than gums formulated with the caffeine split between the coating and the center based upon the following:

Classical pharmacokinetic parameters T-Max and Abs. half-life were greater than pill for both 50 mg pellet and Experiment No. 5 though the level of significant different was much greater for the 50 mg pellet (Experiment No. 5) (a=0.0075 and a=0.005 respectively) than the product of Experiment No. 6 (a=0.05, a=0.15). The Abs. Rate Const. was significantly lower for the pill than for either the 50 mg pellet or

the the product of Experiment No. 6. Again, the level of significant difference was greater for the 50 mg pellet (Experiment No. 5), a=0.005 compared to 0.20 for the product of Experiment No. 6.

7. Combining the conclusions from the two completed caffeine studies, it appears that rate of caffeine uptake in plasma via the various delivery vehicles tested follow this pattern:

Pellet with caffeine all in coating > Pellet with caffeine split between coating and center = Beverages coffee/cola >Pill

Caffeine was chosen as a model for drug delivery tests because it is a food approved, pharmacologically active agent that is readily detected in plasma at a wide range of dosage levels. It is widely consumed via a number of delivery vehicles, including liquids (coffee, cola, and pills). Drugs are administered through different delivery vehicles, two oral delivery vehicles being liquid syrups and pills. Testing caffeinated beverages and pills vs. caffeinated gums should give an indication of how similar drugs administered as liquids or coated pills vs. coated gums could behave.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

The invention is claimed as follows:

1. A method for delivering a medicament to an individual comprising the steps of:

providing a chewing gum that includes a gum center and a coating that substantially surrounds the center, the coating comprising at least 50% by weight of the chewing gum, the coating including a medicament that is designed to be delivered into the systemic system of the individual; and

chewing the chewing gum causing the medicament to enter the systemic system of the individual through an oral mucosa of the individual.

2. The method of Claim 1 wherein the coating includes a high-intensity sweetener.

3. The method of Claim 1 wherein the high-intensity sweetener is chosen from the group consisting of aspartame, sucralose, saccharin, and acesulfame-k.

4. The method of Claim 1 wherein the coating is produced by alternating layers of a powder and a syrup onto the gum center.

5. The method of Claim 1 wherein the gum center includes at least 50% by weight water-insoluble gum base.

6. The method of Claim 1 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

7. The method of Claim 1 wherein the coating has a matte finish.

8. The method of Claim 1 wherein the coating does not include a shellac layer.

9. A chewing gum comprising:

a gum center; and

a coating including a medicament that surrounds the gum center, the coating comprising at least 50% by weight of the chewing gum product, the medicament being designed to be delivered into the systemic system of a patient.

10. The chewing gum of Claim 9 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; stimulants; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

11. The chewing gum of Claim 9 wherein the coating includes a sufficient amount of taste masking agent to provide acceptable organoleptic properties.

12. The chewing gum of Claim 11 wherein the taste masking agent is chosen from the group consisting of: zinc gluconate, ethyl maltol, glycine, acesulfame-k, aspartame; saccharin; fructose; xylitol; isomalt; maltitol; spray dried licorice root; glycerrhizine; sodium gluconate; glucono delta-lactone; ethyl vanillin; dextrose; sucralose; vanillin; and ethyl maltol.

13. The chewing gum of Claim 11 wherein the taste masking agent comprises approximately 30% to about 99% by weight of the coating.

14. The chewing gum of Claim 9 wherein the coating includes approximately 0.5% to about 5% by weight of a high-intensity sweetener chosen from the group consisting of aspartame, sucralose, saccharine, and acesulfame-k.

15. The chewing gum of Claim 9 wherein the gum center includes at least 50% by weight water-insoluble gum base.

16. The chewing gum of Claim 9 wherein the coating does not have a shellac layer.

17. The chewing gum of Claim 9 wherein the gum center and coating are sugar-free.

18. A product including a medicament that is designed to function by being delivered through the systemic system of an individual comprising:

a chewing gum center; and

a coating that at least substantially surrounds the chewing gum center and includes a medicament and a high-intensity sweetener, the coating comprising at least 50% by weight of the product.

19. The product of Claim 18 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; stimulants; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

20. The product of Claim 18 wherein the coating includes a sufficient amount of taste masking agent to provide acceptable organoleptic properties.

21. The product of Claim 18 wherein the taste masking agent is chosen from the group consisting of: zinc gluconate, ethyl maltol, glycine, acesulfame-k, aspartame; saccharin; fructose; xylitol; isomalt; maltitol; spray dried licorice root; glycerrhizine; sodium gluconate; glucono delta-lactone; ethyl vanillin; dextrose; sucralose; vanillin; and ethyl maltol.

22. The product of Claim 18 wherein the taste masking agent comprises approximately 30% to about 99% by weight of the coating.

23. The product of Claim 18 wherein the coating includes approximately 0.5% to about 5% by weight of a high-intensity sweetener chosen from the group consisting of aspartame, sucralose, saccharine, and acesulfame-k.

24. The product of Claim 18 wherein the coating comprises at least 70% by weight powder when it is applied to the gum center.

25. The product of Claim 18 wherein the product is sugar-free.

26. The product of Claim 18 wherein the coating does not have a shellac layer.

27. A method of delivering a medicament comprising the steps of:

providing a chewing gum having a gum center and a coating that substantially surrounds the center, the coating comprising at least 50% by weight of the chewing gum, the coating including a medicament and not including a shellac layer; and

chewing the chewing gum for at least 2 minutes in a buccal cavity of an individual chewing the chewing gum thereby causing the medicament to be absorbed into the systemic system of the individual.

28. The method of Claim 27 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; and cardiovascular agents.

29. The method of Claim 27 wherein the gum center comprises approximately 30% to about 90% by weight insoluble gum base.

30. A method for delivering a medicament to the systemic system of an individual comprising the steps of:

providing a chewing gum product that includes a gum center and a coating having a formulation that includes a medicament, designed to be delivered through the systemic system, and a sufficient amount of a masking agent to provide acceptable organoleptic properties, the formulation comprising at least 50% by weight of the chewing gum product; and

chewing the chewing gum product to cause the medicament to be released from the formulation into the systemic system of the individual through a buccal cavity of the individual.

31. The method of Claim 30 wherein the formulation includes a high-intensity sweetener.

32. The method of Claim 30 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; stimulants; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

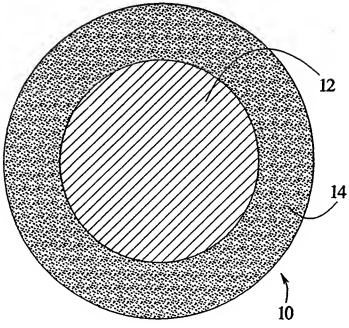
33. The method of Claim 30 wherein the taste masking agent is chosen from the group consisting of: zinc gluconate, ethyl maltol, glycine, acesulfame-k, aspartame; saccharin; fructose; xylitol; isomalt; maltitol; spray dried licorice root; glycerrhizine; sodium gluconate; glucono delta-lactone; vanillin; dextrose; sucralose; and ethyl maltol.

34. The method of Claim 30 wherein the masking agent comprises approximately 30% to about 99% by weight of the coating.

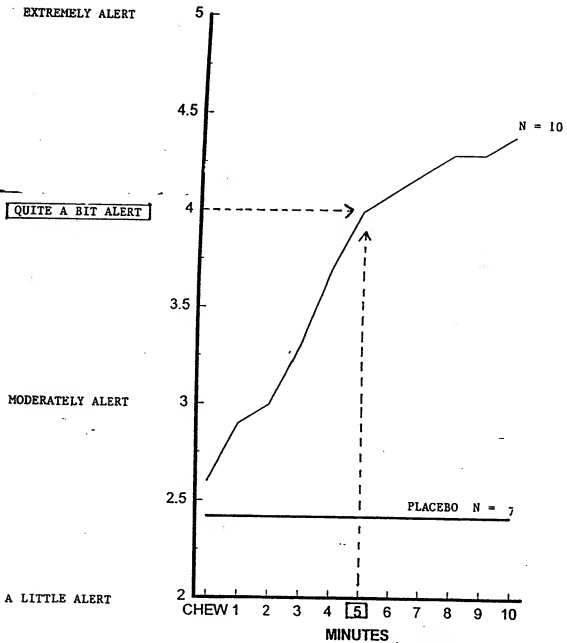
ABSTRACT

Methods and products for delivering a medicament or agent to an individual are provided. The product includes a coating having a medicament or agent. The medicament or agent is present within the coating that surrounds a gum center (the water soluble portion and a water insoluble base portion). By chewing the gum, the medicament or agent is released from the product. Continuing to chew the chewing gum creates a pressure within the buccal cavity forcing the agent or medicament directly into the systemic system of the individual through the oral mucosa contained in the buccal cavity. This greatly enhances the absorption of the drug into the systemic system as well as the bioavailability of the drug within the system.

FIG. 1



STAY ALERT CAFFEINE CHEWING GUM AVERAGE ALERTNESS RESPONSE*



* REFERENCE PANAS FEELING AND EMOTION SCALE

Fig 2

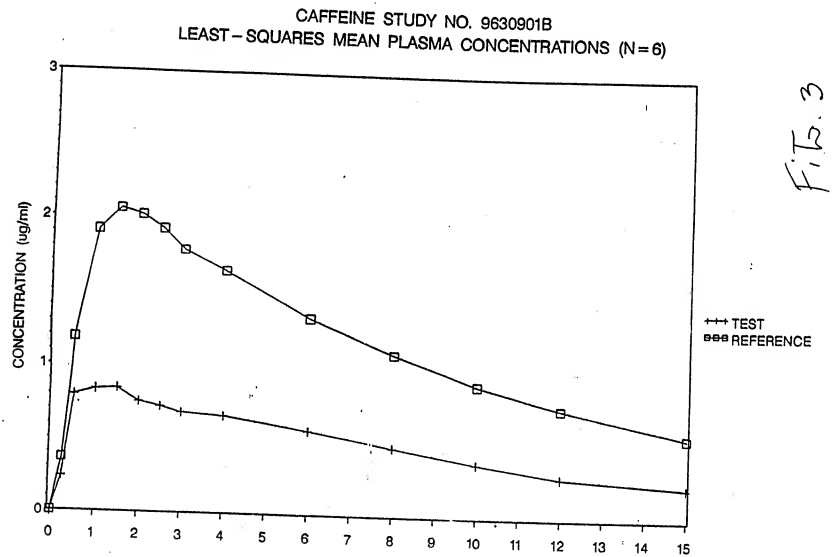

CAFFEINE STUDY NO. 9630901B
LEAST – SQUARES MEAN PLASMA CONCENTRATIONS (N = 6)
CONCENTRATION (ug/ml)
0
1
2
3
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
TEST
REFERENCE

FIG. 3

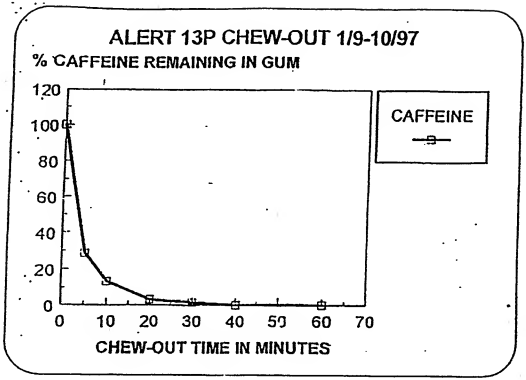

ALERT 13P CHEW-OUT 1/9-10/97
% CAFFEINE REMAINING IN GUM
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
CHEW-OUT TIME IN MINUTES
CAFFEINE

FIG 4

Exhibit D

United States Patent [19]

Cherukuri et al.

[11] **4,317,838**

[45] **Mar. 2, 1982**

[54] **METHOD FOR APPLYING SUGARLESS COATING TO CHEWING GUM AND CONFECTIONS**

[75] Inventors: **Subraman R. Cherukuri; Dominick R. Friello,** both of Danbury, Conn.

[73] Assignee: **Life Savers, Inc.,** New York, N.Y.

[21] Appl. No.: **237,336**

[22] Filed: **Feb. 23, 1981**

Related U.S. Application Data

[63] Continuation of Ser. No. 77,968, Sep. 24, 1979, abandoned.

[51] **Int. Cl.**[3] **A23G 3/30**

[52] **U.S. Cl.** **426/5;** 426/291; 426/292; 426/303; 426/305

[58] **Field of Search** 426/3-6, 426/103, 291, 292, 295, 303, 305, 804, 548, 658

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,304,246	12/1942	Ekert	426/5
2,305,960	12/1942	Frorer	426/5
3,554,767	1/1971	Daum et al.	426/6
4,127,677	11/1978	Fronczkowski	426/5

Primary Examiner—Jeanette M. Hunter

Attorney, Agent, or Firm—Lawrence S. Levinson; Burton Rodney

[57] **ABSTRACT**

An improved method for applying a sugarless coating containing sorbitol to chewing gum pieces and confections by using a single coating syrup containing sorbitol and/or other non-sugar sweetener, an adhesion or binder component, such as gum arabic, a filler-anti-stick component, such as calcium carbonate, and a dispersing agent, such as titanium dioxide.

13 Claims, No Drawings

METHOD FOR APPLYING SUGARLESS COATING TO CHEWING GUM AND CONFECTIONS

This is a continuation of application Ser. No. 077,968, filed Sept. 24, 1979 now abandoned.

FIELD OF THE INVENTION

The present invention relates to an improved method for applying a sugarless coating containing sorbitol in crystalline form, to a chewing gum, confection, and medicinals and therapeutics in the form of pills or tablets, and to any of the above comestibles containing such a sugarless coating.

BACKGROUND OF THE INVENTION

Candy-coated chewing gums have long been a favorite among young and old alike. The candy coatings generally employed are sugar-based and thus are not used as coatings for sugarless gums. The sugar-based coatings may be applied to chewing gum employing procedures such as described in U.S. Pat. Nos. 3,554,767 to Daum et al, 2,304,246 to Ekert, 2,460,698 to Lindhe and 3,208,405 to Beer.

U.S. Pat. No. 4,127,677 to Fronczkowski et al discloses a xylitol coated chewing gum containing from 95 to 99.5% xylitol which may be used as a coating for sugarless gums. However, for various reasons, xylitol containing chewing gums have not received satisfactory consumer acceptance.

Sorbitol, long used as a plasticizer and sweetener, has been suggested as a substitute for sugar in forming sugarless candy coatings for sugarless chewing gums. Unfortunately, however, it has been found that when sorbitol is applied in an aqueous coating solution to chewing gum centers, the sorbitol does not recrystallize to form a thin crystalline coat. Moreover, the chewing gum centers subjected to the sorbitol chewing step stick to one another forming undesirable clumps.

Accordingly, a need exists in the market place for a sugarless coating, preferably free of xylitol, based on the use of sorbitol.

Copending application Ser. No. 12,999, filed Feb. 21, 1979 discloses a method for forming a sugarless candy coating, preferably including crystalline sorbitol, on chewing gums, confections, and generally in the preparation of candy coated pills, tablets and other solid shapes, which method overcomes the problems associated with the application of sorbitol-containing coatings to produce a uniform sugarless coating, with good appearance, and flavor release and having bite-through and chew properties of a soft crystal. The technique employed for forming a sugarless coating on a solid shape to be coated (hereinafter referred to as centers) includes the steps of applying to the centers a first coating syrup which contains a sweetener such as sorbitol and/or other non-sugar sweetener, for example, mannitol or hydrogenated starch hydrolysate, an adhesion or binder component and a film-forming component, to thereby coat the centers with the first coating syrup, the dusting mix including one or more sweeteners, such as employed in the first coating syrup, in powdered form, and a moisture absorbing component, such as mannitol, an anti-sticking component such as calcium carbonate and a dispersing agent such as titanium dioxide, and then preferably applying a second coating syrup to smooth out the coating of the centers and provide a shine thereto, which second coating syrup generally includes ingredients similar to that present in the dusting mix but dispersed in water.

The above technique has proved to be an excellent method, albeit, it usually requires two different types of coating syrups to produce the desired coating. Accordingly, a sugarless coating technique wherein only a single coating syrup is employed would be a tremendous advance over the afore-mentioned prior art as well as over the above-described copending application.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, an improved so-called "one step" or "one syrup" method is provided for forming a sugarless coating on a solid shape to be coated (hereinafter referred to as centers) and includes the steps of applying to the centers a coating syrup which contains a sweetener such as sorbitol and/or other non-sugar sweetener, for example, mannitol or hydrogenated starch hydrolysate, an adhesion or binder component and a film-forming component, an anti-sticking (or filler) component, and a dispensing agent, to thereby coat the centers with the coating syrup, and then applying a dusting mix to the centers coated with the coating syrup, the dusting mix including one or more sweeteners, such as employed in the coating syrup, in powdered form, and a moisture absorbing component, an anti-sticking component and a dispersing agent.

The steps of applying the coating syrup and dusting mix will be repeated, as many times as necessary, to build up a desired coating weight and thickness on the centers.

In carrying out the method of the invention, coating syrup will be formed as an aqueous solution of the (a) sweetener (or bulking agent), (b) adhesion or binder component, (c) an anti-sticking (filler) component, and (d) a dispersing agent.

The sweetener (or bulking agent) (a) may be present in an amount within the range of from about 30% to about 70% , preferably from about 40 to about 60% by weight of the coating syrup; the binder (b) may be present in an amount within the range of from about 5 to about 30%, preferably from about 10 to about 25% by weight of the coating syrup; the anti-sticking (filler) agent (c) may be present in an amount within the range of from about 3 to about 15% and preferably from about 5 to about 10% by weight of the coating syrup; and the dispersing agent (d) may be present in an amount of within the range of from about 2 to about 12%, and preferably from about 3 to about 7% by weight of the coating syrup. The coating syrup will also contain from about 20 to about 70%, and preferably from about 25 to about 65% water.

The coating syrup functions as a wet base layer to which later-deposited dry sweetener or bulking agent (present in the dusting mix) may adhere or be absorbed on to form the desired coating.

Examples of sweeteners or bulking agents suitable for use in the coating syrup may comprise substantially any known sugarless sweetener such as any of the sugar alcohols such as sorbitol, xylitol, mannitol, and combinations thereof, with sorbitol being preferred, as well as maltitol, isomaltitol, hydrogenated starch hydrolysates such as those disclosed in U.S. Pat. No. Re. 26,959 as well as various hydrogenated glucose syrups and/or powders which contain sorbitol, hydrogenated disac-

charides, tri- to hexa-hydrogenated saccharides, and hydrogenated higher polysaccharides and the modified starch hydrolysates disclosed in U.S. Pat. No. 3,556,811 to Smith.

The hydrogenated glucose syrups and/or powders may be produced by catalytic hydrogenation of standard glucose syrups (acid and/or enzyme converted) to the point where all the glucose end groups of the saccharides are reduced to alcohols, that is, dextrose to sorbitol. In the case of hydrogenated glucose syrups, the total solids contents will range from about 72 to about 80% which solids are made of from about 4 to about 20% sorbitol, from about 20 to about 65% hydrogenated disaccharides (that is, maltitol), from about 15 to about 45% tri- to heptahydrogenated saccharides, and from about 10 to about 35% hydrogenated saccharides higher than hepta.

Other sweeteners or bulking agents suitable for use in the coating syrup include, but are not limited to free saccharin acid, sodium, calcium and ammonium saccharin, cyclamate salts, dihydrochalcones, glycyrrhizin, L-aspartyl-L-phenylalanine methyl ester and mixtures thereof.

The adhesion component or binder employed in the coating syrup aids in initially binding the sweetener to the comestible being coated. Examples of binders suitable for use herein include gum arabic, xanthan gum, gum tragacanth, tapioca dextrin, or modified food starch, with gum arabic being preferred.

The moisture absorbing compound suitable for use herein includes mannitol, or dicalcium phosphate with mannitol being preferred especially when sorbitol is employed as the sweetener.

Examples of the anti-sticking compound which may also function as a filler employed in the coating syrup as well as the dusting mix include calcium carbonate, talc, or magnesium trisilicate, with calcium carbonate being preferred.

Examples of the dispersing agent which may be employed in the coating syrup as well as the dusting agent include titanium dioxide, talc or other anti-stick compounds set out above, with titanium dioxide being preferred.

An optional but important component of the coating syrup is the film-forming agent which enables the deposition of a substantially uniform layer of the sweetener on the comestible being coated. Examples of film-forming agents suitable for use herein include gelatin, methyl cellulose, hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and/or carboxymethyl cellulose.

The dusting mix comprises a dry powder mixture containing (a) sweetener (or bulking agent) similar to (and preferably the same as) that employed in the coating syrup, (b) moisture absorbing component, (c) anti-sticking (or filler) component, and (d) dispersing agent. Components (b), (c) and (d) are employed in a weight ratio to sweetener (a) of within the range of from about 5 to about 30(b):1, from about 2 to about 20(c):1, and from about 0 to about 5(d):1. Thus, the sweetener (a) will be employed in an amount within the range of from about 40 to about 90%, and preferably from about 60 to about 85% by weight of the dusting mix, the moisture absorbing component (b) will be employed in an amount within the range of from about 5 to about 30%, and preferably from about 8 to about 20% by weight of the dusting mix, the anti-sticking component (c) will be employed in an amount within the range of from about 2 to about 20%, and preferably from about 5 to about 15% by weight of the dusting mix, and the dispersing agent will be employed in an amount within the range of from about 2 to about 12%, and preferably from about 4 to about 9% by weight of the dusting mix.

As indicated, the sweetener (bulking agent) present in the dusting mix may include any of those employed in the coating syrup and set out above. The preferred sweetener present in the dusting mix will be sorbitol.

In preferred embodiments, the weight ratio of the solids present in the coating syrup to the dusting mix will range from about 5:1 to about 20:1.

Generally, a single deposition of each of the coating syrup and the dusting mix may not be sufficient to provide the desired amount or thickness of coating deposited on the comestible. Accordingly, it usually will be necessary to apply second, third or more coats of each of the coating syrup and dusting mix in order to build up the weight and thickness of the coating to desired levels. However, before applying subsequent layers of first coating syrup, the previously applied layers of coating syrup are allowed to dry, for example, by gently flowing air at a temperature of from about 68° to about 88° F. and having a relative humidity of from about 20 to about 40% and flowing at a volume (36" pan) of from about 400 to about 500 cfm. For example, in coating chewing gum, the applications of coating syrup and dusting mix are continued until the average gum piece weight reaches about 90% of the required coated weight. Thus, if the coating is to comprise about 35% by weight of the coated chewing gum tablet, application of 10 to 12 coats of coating syrup and 7 to 9 coats of dusting mix may be required. The last three coats should preferably be coating syrup by itself, without dusting mix.

It will be appreciated that the number of applications required will also vary depending upon the amount of solids present in the coating syrup, the amount of dusting mix employed, and the type of comestible to be coated.

After a sufficient amount of coating has been applied to the pieces of comestible to be coated, the coating on the pieces will be smooth and polished and otherwise finished without the need for applying a second coating syrup or finishing syrup.

Flavoring in the form of liquid flavor may be added with the coating syrup, while spray dried flavors may be added with the dusting mix. The flavoring will preferably be applied after an initial coating syrup-dusting mix has been applied.

In the case where the comestible to be coated is chewing gum, flavoring may be added to the gum base. The flavoring in the gum center will be present in an amount within the range of from about 0.5 to about 1.5%, and preferably from about 0.7 to about 1.2% by weight of the gum center. The flavoring in the coating will be present in an amount within the range of from about 0.5 to about 5% and preferably from about 1.25 to about 4% by weight of the coating. Such flavoring may comprise oils derived from plants, leaves, flowers, fruit, etc. Representative flavor oils of this type include citrus oils such as lemon oil, orange oil, lime oil, grapefruit oil, fruit essences such as apple essence, pear essence, peach essence, strawberry essence, apricot essence, raspberry essence, cherry essence, plum essence, pineapple essence, as well as the following essential oils: peppermint oil, spearmint oil, mixtures of peppermint oil and spearmint oil, clove oil, bay oil, anise oil, eucalyptus oil, thyme oil, cedar leaf oil, cinnamon oil, oil of nutmeg, oil

of sage, oil of bitter almonds, cassia oil, and methylsalicylate (oil of wintergreen). Various synthetic flavors, such as mixed fruit, may also be incorporated in the chewing gum of the invention with or without conventional preservatives.

Sweeteners suitable for use herein which may be present in the gum center and/or coating may comprise natural or synthetic sugar substitutes.

Where employed, the synthetic sweeteners may be present in the chewing gum center in an amount within the range of from about 0.04 to about 2% and preferably from about 0.4 to about 0.8% by weight of the chewing gum. Examples of synthetic sweeteners suitable for use herein include free saccharin acid, sodium, calcium or ammonium saccharin, cyclamate salts, dihydrochalcones, glycyrrhizic acid and salts, L-aspartyl-L-phenylalanine methyl ester, the sodium or potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (Acesulfone-K), and mixtures thereof.

Where employed, natural sugars and/or natural sugar substitutes may be present in the chewing gum center in an amount within the range of from about 0.05 to about 90%, and preferably from about 10 to about 85% by weight of the chewing gum. Such natural sweeteners suitable for use herein include sugar alcohols, such as, sorbitol, xylitol, mannitol, isomaltitol, or maltitol. If desired, sugars such as sucrose, or dextrose may also be employed.

The gum base will be present in an amount within the range of from about 10 to about 60%, and preferably from about 15 to about 45% by weight.

In general, the gum base is prepared by heating and blending various ingredients, such as natural gums, synthetic resins, waxes, plasticizers, etc., in a manner well known in the art. Typical examples of the ingredients found in a chewing gum base are masticatory substances of synthetic origin such as styrene-butadiene copolymer, isobutylene-isoprene copolymer, polyisobutylene, polyethylene, petroleum wax, polyvinyl acetate, as well as masticatory substances of natural origin such as rubber latex solids, chicle, crown gum, nispero, rosidinha, jelutong, pendare, perillo, niger gutta, tunu, etc. The elastomer or masticatory substance will be employed in an amount within the range of about 5 to about 15%, preferably from about 8 to about 12%, and optimally from about 9 to about 11% by weight of the gum base composition.

The gum base may also include solvents, detackifiers, waxes, softening agents, lubricants, fillers, emulsifiers, colorants, antioxidants and/or texturizers, bulking agents and other conventional ingredients as will be apparent to those skilled in the art. Examples of typical gum bases suitable for use herein are disclosed in U.S. Pat. Nos. 3,052,552 and 2,197,719.

As indicated, in addition to chewing gum, the comestible to be coated may include any edible solid, such as candies, including hard candies and pressed candies, jelly beans, peanuts, other confections, as well as pills, tablets or other solid dosage forms for medicinal or therapeutic use.

A preferred coating, in accordance with the present invention, for a sugarless chewing gum will have the following composition.

Ingredient	Parts by weight of coating
Sorbitol	45 to 90
Mannitol	2 to 25
Gum arabic	0.25 to 3
Calcium carbonate	2 to 20
Titanium dioxide	0.1 to 5

The following Examples represent preferred embodiments of the present invention.

EXAMPLES 1 TO 3

Sugarless-coated sugarless chewing gums having center or core portions as shown in Table I and coatings as shown in Table II below are prepared as follows.

TABLE I

Composition of Gum Center or Core (present in all chewing gum Examples)

Ingredient	Parts by Weight
Gum base	24
Sorbitol-powder	49
Sorbitol liquid (68–70% sorbitol)	25
Yelkin	0.5
Flavor	2

TABLE II

Composition of Various Coating Mixtures Required for Forming Coating on Gum Centers of Table I

	Parts by Weight Example No.		
	1	2	3
Coating Syrup			
Gum arabic solution (48%)	18	20	24
Gelatin solution (20%)	0	30	15
Sorbitol liquid (68–70%)	55	50	60
Hydrogenated starch hydrolysate	—	30	10
Mannitol	7	6	5
Calcium carbonate powder	7	8	5
Titanium dioxide powder	5	4	6
Hot water (160° F.)	9	11	13
Color (as needed)			
Dusting Mix			
Sorbitol (crystalline powder)	70	70	70
Mannitol powder	15	15	15
Calcium carbonate powder	7.5	10	5
Titanium dioxide powder	7.5	5	10

The chewing gum centers are prepared as follows: Gum base is melted and maintained at a temperature within the range of 150°–175° F. Softener is added and then the solid sugar alcohols are added slowly with stirring. Thereafter, liquid flavor is added and the mixture is stirred until homogeneous. Sugar alcohols are slowly added and then artificial and/or natural sweetener (where employed).

Where spray dried flowers are employed, they are added with the artificial sweeteners.

The above mixture is stirred until homogeneous, cooled, rolled and scored and individual pieces or pillows are produced.

The coating mixture is prepared by mixing the various ingredients, under heating if necessary, to form a well-mixed suspension.

The dusting mix is prepared by simply mixing the various ingredients and until a substantially homogeneous mixture is formed.

The gum centers to be coated are placed in a standard revolving coating pan. The gum pieces are dedusted using cool dry air. The coating syrup mixed and warmed to a temperature of 120° F. is applied to the gum pieces. After about 2–3 minutes, the dusting mix is applied to the gum pieces coated with the coating syrup. The gum pieces are allowed to cool for 2 minutes to absorb the dusting mix. The gum pieces are then dried by contact with gently flowing air at a temperature of about 78° F., and having a relative humidity of about 30% and at a volume of air (36" pan) of about 450 cfm, for 2 minutes.

The above coating steps are repeated until the weight of an average gum piece reaches about 90% of the required coated weight. For example, if the required coated weight is 35%, 7 to 10 applications of the dusting mix are needed (the last 3 applications are of other coating syrup without the dusting mix) to reach an average piece weight of 1.5 g.

The so-coated gum pieces may then be polished and otherwise finished employing conventional means to produce sorbitol coated sugarless chewing gum having a soft chew with good sweetness and flavor release properties.

EXAMPLES 4 AND 5

Sugarless coated sugarless candy, having a center or core portion as shown in Table III below and a coating as shown in Table II of Example 1, is prepared employing the following procedure.

TABLE III

Compositon of Candy Center	
Ingredient	Amount (Parts by Weight)
Hydrogenated starch hydrolysate syrup (78% solids,including 6% sorbitol and 50% mannitol)	97
Sorbitol syrup	2
Malic acid	1
Cherry Flavor	0.25
Color	0.4

The hydrogenated starch hydrolysate and sorbitol syrups are fed into the top of a mixing kettle and are cooled under constant slow agitation to 330°–335° F. The coloring agent is added at 280°–300° F. The mix is dropped at 25" Hg and held under vacuum for 10 minutes. The hot mix is then transferred to a mixing table where malic acid and flavor are added with mixing. The candy mix is allowed to cool to 160°–170° F. and is tabletted.

The coating is applied as described in Examples 1 to 3 to produce a pleasant tasting sugarless coated sugarless candy.

In a manner similar to that described in Examples 1 to 5 any type pill or tablet or other solid shape may be coated with a sugarless coating in accordance with the present invention.

What is claimed is:

1. A method for preparing a sugarless coated chewing gum or candy, which comprises the steps of applying to center portions of said chewing gum or candy a coating syrup comprising an aqueous solution of from about 30 to about 70% by weight of a normally sweet non-sugar hygroscopic material selected from the group consisting of sorbitol, mannitol, maltitol, isomaltitol, hydrogenated starch hydrolysate and mixtures thereof, from about 5 to about 30% by weight of a binder, from about 3 to about 15% by weight of an anti-sticking compound, and from about 2 to about 12% by weight of a dispersing agent and applying to said so-treated center portions a coating dusting mix comprising said normally sweet non-sugar hygroscopic material in dry form, at least a portion of said dry hygroscopic material being absorbed on the coating syrup applied to said center portions to form a coating on said center portions.

2. The method as defined in claim **1** wherein said steps of applying said coating syrup and then applying said coating dusting mix are repeated, as necessary, to build up a coating of desired thickness on the center portions.

3. The method as defined in claim 2 further including the step of applying said coating syrup as the last 2 to 4 coats to said center portions previously coated with said coating syrup and said coating dusting mix, said lastly applied coating syrup comprising said normally sweet hygroscopic material and serving to smooth out and providing a shine to the coating of said normally sweet hygroscopic material previously applied to said center portions.

4. The method as defined in claim **1** wherein said coating dusting mix contains a moisture absorbing agent, an anti-sticking agent, and a dispersing agent.

5. The method as defined in claim **1** wherein said coating syrup comprises liquid sorbitol, gum arabic solution, calcium carbonate, titanium dioxide and mannitol, and said coating dusting mix comprises sorbitol powder, mannitol powder, calcium carbonate and titanium dioxide.

6. A method as defined in claim **1** wherein said center portion comprises chewing gum or candy.

7. The method as defined in claim **1** wherein said center portion is sugarless chewing gum.

8. The method as defined in claim **1** wherein said coating syrup further includes a film-forming agent which comprises gelatin, methyl cellulose, hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and/or carboxymethyl cellulose.

9. The method as defined in claim **1** wherein said binder for imparting cohesivity to the coating ingredients is gum arabic, xanthan gum, gum tragacanth, tapioca dextrin, or modified food starch.

10. The method as defined in claim **1** wherein said anti-sticking agent is calcium carbonate, talc, or magnesium trisilicate.

11. The method as defined in claim **1** wherein said dispersing agent is titanium dioxide.

12. The method as defined in claim **1** wherein said center portion is candy.

13. The method as defined in claim **1** wherein said center portion is chewing gum and said coating applied is comprised of sorbitol as said hygroscopic material, gum arabic as a binder, calcium carbonate as an anti-sticking-diluent compound, titanium dioxide as a dispersing agent and mannitol as a moisture absorbing agent.

* * * * *

Exhibit E

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A23G 3/30 — A1

(11) International Publication Number: **WO 99/44436**

(43) International Publication Date: 10 September 1999 (10.09.99)

(21) International Application Number: PCT/DK99/00108

(22) International Filing Date: 3 March 1999 (03.03.99)

(30) Priority Data:
0296/98 4 March 1998 (04.03.98) DK

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(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: A COATED CHEWING GUM, A METHOD FOR PREPARATION THEREOF AND THE USE OF ONE OR MORE ACTIVE SUBSTANCE(S) IN SOLID FORM

(57) Abstract

A coated chewing gum comprising a core of chewing gum and a coating comprising a coating material and one or more active substance(s) in solid form. The use of an active substance in solid form in the coating of a coated chewing gum provides a fast onset of the effect, a better stability of the active substance, and an increased effect thereof in all chewing phases.

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A Coated Chewing Gum, a Method for Preparation thereof and the Use of One or More Active Substance(s) in Solid Form

Technical Field

The present invention relates to a coated chewing gum comprising a core of chewing gum and a coating comprising a coating material as well as one or more active substance(s) in solid form. Furthermore, the invention relates to a method for the preparation of a coated chewing gum and the use of one or more active substance(s) in solid form in the coating of a coated chewing gum.

Technical Background

Coated chewing gum is prepared by coating a core of chewing gum with a number of layers of coating. The coating most often takes place in rotating coating kettles in which cores of chewing gum are rotated and coating suspension is applied in small portions that disperse evenly over the surfaces of the cores. Subsequently, the coated cores are dried by means of air.

These coating operations may be applied in up to approx. 90 increments until the preferred coating thickness is obtained, and the product has the preferred measures and the preferred weight.

The coating suspension is often an aqueous solution of a sugar or the like applied at an elevated temperature to ease the coating process.

In order to provide a fast flavour onset, often one or more flavour(s) is/are applied and possibly other active substances between the applications of the coating suspension. The active substance(s) is/are added in liquid form in one or more increment(s).

A chewing gum with a completed coating is normally finally treated with a surface layer of a wax or the like.

The tablets with a completed coating are then subjected to a hardening process during the following approx. 8 weeks. Sugar alcohols such as sorbitol and xylitol thus form crystals whereby the chewing gum obtains a harder and a "crunchy" coating. The crystallisation process also provides a more porous coating structure. Thus, a migration of water, moisture and flavour takes place through the formed micro channels.

This causes the chewing gum to gradually lose its flavour, ethereal oils, if any, are oxidised, and the chewing gum loses moisture and gets harder.

Furthermore, the use of active substances in liquid form in the coating layers has the disadvantage that some of the active substances are lost to the surroundings during the coating process.

It has now been found that by using active substances in solid form in the coating layers of conventional chewing gum, an increased stability of the active substance is obtained. Furthermore, a faster onset of the effect is achieved, and by using flavour in solid form, a longer lasting explosion of taste compared with chewing gum coated with a liquid flavour. Finally, according to the invention, a more environmentally desirable manufacturing process is obtained since the use of an active substance in solid form causes less evaporation of volatile substances.

Disclosure of the Invention

Thus, the invention relates to a coated chewing gum comprising a core of chewing gum and a coating which comprises a coating material, and one or more active substance(s), which chewing gum is characterised in that the active substance(s) is/are added in solid form.

Furthermore, the invention relates to a method for the preparation of a coated chewing gum according to the invention, which method is characterised in that it comprises the following steps:

1) preparation of a core of chewing gum in a manner known *per se*,

2) preparation of a coating suspension, also in a manner known *per se*,

3) repeated applications of the coating suspension onto the cores of chewing gum also in a manner known *per se*, preferable at a temperature in the interval 30-90°C, preferably 35-75°C,

4) Applying on the coating of one or more active substance(s) in solid form in one or more increment(s) after the application of the coating suspension, and optionally repeating step 3) and 4)

5) optionally, application of one or more liquid active substance(s) in one or more increment(s) between the applications of the coating suspension,

6) optionally, finally application of a surface layer.

Applying of the solid active substance(s) is/are preferable performed without drying of the coating suspension in order to enable adherence of a substantial amount of the substance(s) in solid form to the coating. The drying time for the coating suspension depends on the specific coating formulation, however, the active substance(s) is/are added to the coated chewing gum substantially without delay after the coating processes are finished. If desired, the coated chewing gum may be wetted before adding the active substance(s) in solid form in case the coating has been allowed to dry for too long time whereby the coated chewing gum is no longer sticky.

The coating process may be repeated as many times as needed in order to obtain the desired thickness of the coating. In the coating process, the active substance(s) in solid form may be added between one or more of the ordinary coating processes. The last layer of the coating process may also include the active substance(s) in solid form. It is also within the present invention to use different active substances in solid form in the same coating layer or use one active substance in one layer, and a second active substance in another layer. Such combinations of active substances may be flavour and high potent sweeteners or a medicament together with an substance decreasing an undesirable taste of the medicament.

As the active substance(s) is/are located in the outer part of the coating, the active substance(s) is/are exposed to the consumer within a short period of chewing. Accordingly, in a further embodiment, the invention relates to the use of one or more active substance(s) in solid form in the coating of a coated chewing gum in order to obtain a fast onset of the effect.

A further advantage of the admixture of the active substance(s) in solid form is that the solid form is more resistant to decomposition. Accordingly, the invention also relates to the use of one or more active substance(s) in solid form in the coating of a coated chewing gum in order to obtain a better stability of the active substance(s).

Finally, the invention relates to the use of one or more active substance(s) in solid form in the coating of a coated chewing gum in order to obtain an increased effect of the active substance(s) in all chewing phases.

Brief Description of the Drawing

The invention is further illustrated by means of the drawing, in which

Fig. 1 shows the release of flavour as a function of time by using menthol/-anethol/eucalyptus flavour in encapsulated form and liquid form, respectively,

Fig. 2 shows the release of flavour as a function of time by using the same amount of eucalyptus/anethol/menthol flavour in encapsulated form and liquid form, respectively,

Fig. 3 shows the release of flavour as a function of time by using liquid eucalyptus/anethol/menthol flavour and with and without encapsulated menthol,

Fig. 4 shows the stability of chewing gum with apple/cinnamon flavour with encapsulated and non-encapsulated aspartame, respectively, in suspension form in the coating,

Fig. 5 shows a flavour profile in the initial phase of chewing gum with fruit flavour (lemon/orange/mango) with and without encapsulated citric acid in the coating,

Fig. 6 shows a flavour profile in the initial phase of a chewing gum with fruit flavour (lemon/orange/mango) with and without encapsulated "cooling agent" in the coating,

Fig. 7 shows the same in the intermediate phase,

Fig. 8 shows the same in the end phase,

Fig. 9 shows a flavour profile in the initial phase of chewing gum with menthol/-anethol/eucalyptus flavour and with encapsulated thyme extract in the coating,

Fig. 10 shows the same in the intermediate phase,

Fig. 11 shows the same in the end phase,

Fig. 12 shows a flavour profile in the initial phase of chewing gum with menthol/-anethol/eucalyptus flavour and with encapsulated extract of black pepper in the coating,

Fig. 13 shows the same in the intermediate phase, and

Fig. 14 shows the same in the end phase.

The scope of the invention will appear from the detailed description below. However, it should be understood that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the scope of the invention will become apparent for those skilled in the art from the detailed description.

Detailed Description of the Invention

The active substances are selected among flavours, acids, salts, high potent sweeteners, and functional substances.

Aromas, which may be incorporated into the chewing gum according to the invention, are selected among natural, naturally identical or synthetic flavours, as well as plant extracts. Examples of applicable flavours are for example peppermint, periwinkle, eucalyptus, spearmint, anethol, menthol, powdered anise, and fruit flavours such as orange, lemon, mango, pineapple, lime, strawberry, cherry, black currant, blueberry, raspberry, wild berry, cranberry, apple, pear, banana, prune, and plum flavour, etc.

The plant extracts which may be applied instead of or together with one or more of the above-mentioned flavour(s) are preferably selected among extracts of liquorice, coffee, tea, herbs such as sage, thyme, basil, bergamot, balm, valerian, camomile, lavender, aloe vera, and spices such as pepper, cinnamon, capsicum, paprika, tarragon, fennel, mustard, dill, caraway, parsley, tomato, etc.

The use of plant extracts in coated chewing gum provides the possibility of preparing novel combinations of flavour and new flavour experiences.

In a preferred embodiment of the invention the active substance(s) is/are a natural vegetable flavouring agent such as fruit and herbs. Accordingly the substance may be selected among coconut, grape fruit, orange, lime, lemon, mandarin, pineapple, strawberry, raspberry, mango, passion fruit, kiwi, apple, pear, peach, apricot, cherry, pineapple, grapes, banana, cranberry, blueberry, black currant, red currant, gooseberry, and lingonberry, thyme, basil, valerian, fennel, parsley, camomile, tarragon, lavender, dill, cumin, bergamot, sage, aloe vera, spearmint, peppermint, eucalyptus and mixtures thereof.

It is furthermore an advantage that the natural flavouring agent is dried. A dried agent may have a more intense flavour and may further increase the stability of the flavour because many of the notes of the taste are still present in the more or less intact cells of the fruit or herb. The limited content of water is also an important factor with respect to stability.

In a further aspect, the water content of the natural flavouring agent is less than 75% by weight, such as less than 60%, preferable less than 40%, more preferred less than 30%, such as less than 25%. However, in situations where a less water content is

desired (for stabilty reasons or with respect to have an increased flavour sensation), the water content of the natural flavouring agent is less than 20% by weight, such as less than 15%, more preferred less than 10% such as between 1.5-7%, more preferred between 2-6%.

In a preferred embodiment, the natural flavouring agent is freeze-dried.

The natural flavouring agent in solid form may be in the form of a powder, slices or pieces, or combinations thereof. When a natural vegetable flavour is used, it is generally accepted or even desired that a feeling of small pieces of the flavour agent be recognised by the consumer in the chewing process. Accordingly, the natural flavouring agent may be in a form where the particle size is up to 3mm or even more. However smaller pieces are preferred and in a further aspect, the particle size is less than 3mm, such as less than 2mm, more preferred less than 1mm, calculated as the longest dimension of the particle.

In other situations it may be an advantage to have different sizes of the particles and an example is wherein the natural flavouring agent is in a form where the particle size is from about 3μ to 2mm, such as from 4μ to 1mm. However, the skilled person may select any combination dependent on the desired final properties of the coated chewing gum.

As seeds from fruits may have a special flavour, the natural flavouring agent may comprise seeds from a fruit e.g. from strawberry, blackberry and raspberry, and which seeds are substantially intact.

In a still further aspect of the invention, the natural vegetable flavouring agent also provides the gum formulation with natural colour. With seeds of a vegetable or fruit flavouring agents such as strawberry and/or orange, it has been possible to obtain a marbling colouring of the chewing gum as well as a uniform colouring. Accordingly, in a further aspect of the invention, the active substance in solid form may be a colouring agent.

Various acids may also be applied as active substances, such as citric acid, malic acid, tartaric acid, lactic acid, and ascorbic acid or any other acid allowed in food and which is suitable. These may most conveniently be applied together with chewing gum with fruit flavour in order to obtain an improved freshness during the first phase of the chewing period.

Furthermore, according to the invention, instead of or together with one or more of the above-mentioned active substance(s), salts may be applied, such as sodium chloride, potassium chloride, ammonium chloride, sodium bicarbonate, and carbamide. Hereby an improved chewing gum taste during the initial chewing period is obtained, and in case of sodium bicarbonate and carbamide also an improved dental care effect.

In order to obtain a sweet taste during the initial chewing period, together with or instead of one or more of the above-mentioned active substance(s) sweeteners may be incorporated in the coating, preferably highly potent sweeteners. Especially suitable sweeteners are e.g. aspartame, acesulfame K, saccharin, cyclamate, neohespiridine, thaumatin, glycyrrhizin, and salts thereof, monellin, sucrolase, and alitame.

Finally, in order to obtain a specific effect together with or instead of one or more of the above-mentioned active substance(s), one or more functional substance(s) can be incorporated in the coating such as vitamins and nutrients, "cooling agents", flavour enhancers, enzymes, agents for care and treatment of the oral cavity, antiseptic agents, pharmaceuticals and herbal medicine.

"Cooling agents" and flavour enhancers are substances manufactured by so-called "flavour houses", and which substances are also known as "flavour enhancer", "cooling flavour", "physcol", "optacool", and the like. They are applied in order to make the taste stronger and fresh.

Examples of cooling agents are e.g. lactic acid menthyl ester, disclosed in EP 0794169 A1, mono menthylsuccinate, and salts thereof, disclosed in WO97/07771, and 4-(1-menthoxymenthyl)-2-phenyl-1.3-dioxolan and derivatives thereof, disclosed in US 5,545,424.

Among the vitamins and the nutrients that may be incorporated in the chewing gum according to the invention special mention can be made, without limitation, of the vitamins A, B_1, B_2, B_5, B_6, B_{12}, D_3, E, K, folic acid, niacin, biotin, β-carotene, ascorbic acid, and salts thereof, amino acids, glycerophosphates, minerals in the form of salts, complexes and compounds containing calcium, phosphorus, magnesium, iron, zinc, copper, iodine, manganese, chromium, selenium, molybdenum, potassium, sodium, or cobalt and ubiquinon.

Among agents for the care and treatment of the oral cavity, special mention may be made of hydrogen peroxide, carbamide and carbamide releasing compounds, CPP (caseinphosphopeptide), fluorine compounds such as sodium fluoride, sodium monofluorophosphate, and stannofluoride, arginine, zinc compounds, strontium chloride and potassium nitrate.

Among antiseptic agents, special mention may be made of guanidine and biguanidine, such as chlorhexidine acetate, quaternary ammonium compounds such as benzalkonium chloride, cetylpyridinium chloride, and cetrimide, phenols such as tymol, triclosan, parachlorophenol, and cresol, hexachlorophen as well as salicylanilide compounds.

Enzymes may also be incorporated in the chewing gum according to the invention, e.g. papain, trypsin, amyloglucosidase, lactase, glucoseoxidase, streptokinase, streptodornase, dextranase, and mutanase.

Among pharmaceuticals, special mention may be made of caffeine, salicylic acid, and derivatives thereof, such as acetylsalicylic acid, choline salicylate, and magnesium salicylate, paracetamol, salts of pentazocine, buprenorphine, and buprenorphine hydrochloride, codeine hydrochloride and phosphate, morphine and salts thereof, methadone hydrochloride, ketobemidone, β blockers, calcium antagonists, verapamil hydrochloride, verapamil, nifedipine, nitroglycerin, erythrityl tetranitrate, strychnine and salts thereof, lidocaine, tetracaine hydrochloride, etorphine hydrochloride, atropine, insulin, alfa-amylase, polypeptides such as oxytocin, gonadorelin, and LHRH, desmopressin acetate (DDAVP), isoxsuprine hydrochloride, ergotamine compounds, chloroquine phosphate and sulfate, isosorbide, demoxytocin, heparin, lupeol,

sucralfate and salts thereof, nicotine and salts and derivatives thereof, lobeline, cinnarizine, dimenhydrinate, difenhydramine, cyclizine, scopolamine, miconazole, nystatin, metronidazole, hydrocortisone, astemizole, benzocaine, glibenglamide, onsaedantronum, acyclovir, sumatriptan, tropisetron, pizotifen, cisapride, domperidone, itraconazole, omeprazole, terfenadine, fluconazole, naratriptan, zolmiriptan, rizatriptan, eletriptan, almotriptan, sildenafil, tolfenamic acid, tramadol, cetirzine, and loratidine.

Among herbal medicine special mention may be of ginkgo biloba, ginseng, saw palmetto, stevia, ginger, propolis, echinacea, St. John's Wort, Siberian ginseng, guarana, and garlic in the form of drugs, extracts or in purified form.

Furthermore, it is possible by means of the present invention to add substances, which cannot resist the thermal and mechanical influences that normally occur during the manufacturing of cores of chewing gum, such substances being certain vitamins, enzymes, and pharmaceuticals.

The active substance(s) is/are added in the form of dry active substance, preferably spray-dried active substance, or in the form of encapsulated active substance. In a preferred embodiment of the present invention, the active substance is present in an encapsulated form. The active substance is preferably present in the form of a powder with particles having a size of 3-300 µm.

The use of encapsulated active substance provides a larger stability of the substance, and the active substance migrates very slowly to the surface of the coated chewing gum. Furthermore, the contact of the encapsulated active substances with the air is limited, whereby possible oxidation processes take place very slowly. The latter are of particular significance in connection with flavours, especially in the form of ethereal oils, such as peppermint, lemon, lime, and orange.

In addition, by encapsulating the active substance, it is achieved that its reaction with other substances is prevented, substances like e.g. sodium bicarbonate with acid and aspartame with aldehyde-containing flavours, and especially in case of substances with an unpleasant taste, e.g. certain pharmaceuticals, the taste may be camouflaged.

In addition, it has been found that by chewing chewing gum that is coated with encapsulated flavour, not only a strong taste explosion is achieved, but also an enhanced taste in all chewing phases. The latter is due to the fact that flavour capsules from the coating layer of the chewing gum are opened both during the initial chewing and in following chewing period.

Furthermore, using an encapsulated active substance may prevent a discoloration of the coating, e.g. plant extracts such as thyme or black pepper. Finally, it may be desirable to prevent water-solubility, e.g. in connection with the use of acids and salts as the active substance.

When an encapsulated active substance is used, conventionally used encapsulation agents are used as the encapsulation agent, for instance, but without limitation, fatty substances, waxes, gelatin, gum arabic, starch, cellulose, cellulose derivatives, shellac, polyvinyl acetate (PVA), polyethylene (PE), casein, zein, B cyclodextrine, silica, yeast cells, and a mixture of the above encapsulation agents. Preferred encapsulation agents comprise fatty substances such as hydrogenated soy bean, cottonseed, coconut, sunflower, palm kernel, rapeseed, and ricinus oil, or waxes such as bees' wax, candelilla wax, carnauba wax, paraffin wax, and polyethylene wax, etc. Especially preferred is the use of a mixture of hydrogenated rape oil and carnauba wax.

Encapsulated flavour and methods for encapsulation are known from, e.g., EP 0 170 752 A2, EP 0 453 397 A1, EP 0 455 598 B1, and US 4,386,106.

In a particularly preferred embodiment of the coated chewing gum according to the present invention, the coating also comprises besides the coating material as well as one or more active substance(s) in solid form, one or more liquid active substance(s). This provides a larger flexibility of the process of chewing gum manufacture, and, when encapsulated active substance is concerned, a reduction in costs, since the encapsulation makes the process more expensive, and it is thus reserved for only the most sensitive active substances.

In one embodiment of the invention, the coating suspension comprises an aqueous solution of a sugar, a sugar alcohol, an artificial sweetener or mixtures thereof, preferably an aqueous solution of saccharose, dextrose, sorbitol, xylitol, tagatose, mannitol, maltitol, isomalt, aspartame, acesulfame K, saccharin, cyclamate, thalline, and neohespiridine.

The coating suspension is applied in approx. 2 to 90 increment(s), preferably in approx. 30-60 increments to achieve a uniform coating with a suitable thickness.

The active substance(s) is/are applied by sprinkling or by blowing the substances into the rotating kettles a number of times such as from 1 to 10 times between the dosages of the coating suspension, preferably approx. 1 to 4 times to achieve a suitable effect.

The following is a general description of the preparation of chewing gum.

Preparation of Chewing Gum

The preparation process comprises the following:

Mixing of conventional chewing gum components in kneading kettles (mixers) with strong horizontally placed Z-shaped arms, which processes the raw materials and produces a homogeneous gum mass.

The kneading kettles are heated to a temperature of 30-80°C, typically approx. 45°C. The mixing process starts with gum base quantities that have been weighed out, and the processing of these lasts for 1-20 minutes, typically approx. 10 minutes. Then one or more sweetener(s) in powder form or in liquid form is/are added. The dosage of sweeteners and the following processing last from 1 to 20 minutes, typically approx. 7 minutes.

Then the flavours and the remaining components are added and kneaded for a further 1 to 10 minutes, typically approx. 5 minutes. The admixture of flavours and the remaining components may also take place in the beginning of the kneading process,

i.e. before the admixture of the sweeteners. It is also possible to add flavours in two or more portions during the kneading process.

When the kneading is completed, the kneading kettle is tipped, and the gum mass is taken out into carts, onto trays or the like.

The next process is the forming of the chewing gum. Before the forming can take place, the chewing gum mass, however, must be cooled. When taken out, the chewing gum mass has a temperature of 50-70°C, and in order to form the chewing gum, the temperature must be reduced to 30-45°C. The cooling of the chewing gum either takes place by storing the chewing gum mass in carts or on trays for quite a long time or by transporting a thin chewing gum carpet through a cooling tunnel.

The forming of the chewing gum may take place by extrusion through a specially formed nozzle, or the chewing gum may be formed after extrusion by means of rollers, punching machines, tentering wheels, and the like.

The chewing gum may be formed into cores, sticks, balls, cubes, cylinders, and many other shapes.

In order to prevent the chewing gum from sticking to the rollers and other tools, the chewing gum is frequently powdered with a powder, which may consist of i.a. icing sugar, talc, corn flour, and the like.

The formed chewing gum can be cooled immediately to room temperature in a cooling tunnel and be packed (especially in case of bubble gum and soft bubble gum), or the cooling may take place on trays at the store for semimanufactured products at a controlled temperature and moisture.

The formed and cooled chewing gum is then treated by means coating and polishing processes before the packing.

Coating and Polishing of Cores of Chewing Gum

The coating of cores takes place in tilted, round or horizontally placed cylindrical coating kettles that rotate during the whole process. The coating kettles are made from copper, stainless steel or fiberglass-reinforced polyester, and are often equipped with a piping system that supplies and exhausts air and doses the coating suspension.

The coating process may take place as follows:
Cores of chewing put into movement in rotating coating kettles are added to the coating suspension in small portions that disperse evenly over the surfaces of the cores after a short or long smoothing out time. (The smoothing out time is the period of time during which the suspension disperses over the cores, approx. 10-90 seconds, preferably approx. 30-60 seconds). Afterwards the cores are dried by means of air. The operation is repeated up to 90 times, preferably approx. 30-40 times, until the cores are completely covered and have the preferred measure and the preferred weight.

In order to ease the coating process of chewing gum, a suspension is used which is heated up to 90°C, preferable up to about 75°C, and air which is heated up to at least 35°C such as about 40°C.

Between the dosages of the coating suspension, one or more active substance(s) in solid form is/are added in one or more increment(s) in order to provide the chewing gum with a fast effect, e.g. flavour release during the chewing. It is an important aspect of the invention that the drying period is extended to after applying the active substances. When the active substances are added just after the coating process is completed, the coating suspension is still soft and the active substances may be more or less embedded in the coating in the solid form. The skilled person will be able to estimate or to establish by a simple test when the active substance should be added for obtaining a sufficient adherence of the active ingredient to the coating.

As appears from the Examples, the drying period is 0 seconds, however, drying periods up to 50 seconds such as up to 25 seconds are within the present invention and even longer periods may be acceptable depending on the drying properties of the

coating suspension, the particle size of the active substance as well as whether it is desired that the active substance should be fully embedded in the coating or should form a superficial layer on the coating.

Furthermore, between the dosages of the coating suspension and the addition of one or more active substance(s) in solid form, one or more active substance(s) in liquid form may be added.

In order to achieve a neat and smooth surface of the chewing gum tablets with the completed coating, these may subsequently be subjected to a polishing. The polishing also takes place in rotating coating kettles in which a polishing suspension or a polishing powder is added to the coated cores in one or more portion(s). The polishing suspension often consists of wax, emulsifier, shellac, gum arabic, water, etc. The polishing powder often consists of wax only, or of wax mixed with emulsifier, gum arabic or talc, etc.

The present invention is further illustrated below by means of some examples.

Examples

As a starting point, partly sugar-containing, partly sugar-free cores of chewing gum are used which are rolled out into sheets by means of stamping rollers, i.e. coherent sheets of cores of chewing gum which have a weight of approx. 0.9g/piece.

A coating kettle DRIA 1200, supplied by Driam Metallprodukt GmbH, Germany, is used for the coating of the above-mentioned cores. DRIA 1200 is a horizontally placed and cylindrical kettle intended for the coating of 50kg of chewing gum cores. The equipment has computer controlling of the amount of dosages of liquid and solid substances as well as controlling of the smoothing out times, the drying times, air quantities, the temperature of the drying air, and the airflow direction. For dosage of an active substance in a solid form, a pneumatic conveyor having a dispersing arm which ensures an even dispersion of the powder over all the tablets. The coating kettle can be set at various velocities from 1 to 15 rpm.

During the coating process, 50kg of chewing gum cores are filled into the coating kettle that can be set to a rotation of 8 rpm. During this rotation, the cores of chewing gum are separated from each other. Drying air is applied to the equipment, and surplus talc, which has been added during the rolling out of the cores of chewing gum, is removed. This separation and blowing through of air last for approx. 5 minutes.

Then the rotation speed of the coating kettle is increased to 11 rpm, and the first dosage of the coating suspension may take place.

It is also possible to use small (2kg) or large (100kg) tilted, round coating kettles and sprinkle active substance in solid form manually in 1-10 increment(s) between the dosages of the coating suspension. Dosage of active substance in more increments ensures an even dispersion of the powder over all the cores of chewing gum.

For the coating of sugar-containing cores of chewing gum, a saccharose suspension was used in the following examples, and a sorbitol suspension was used for the coating of sugar-free cores.

In the following embodiments, the coating suspension had the following composition:

1. Saccharose suspension

Sugar juice (70%)	94.45 %
Water	4.68 %
Gelatine (Bloom value 120-160)	0.87 %
Total	100.00 %

2. Sorbitol suspension

Sorbitol liquid/neosorb 70/02	97.86 %
Water	1.59 %
Titanium dioxide	0.55 %
Total	100.00 %

The Examples 1, 2, and 3, shows conventional coating of sugar-containing and sugar-free cores of chewing gum, respectively.

Example 1

Coating in DRIA 1200 equipment of 50kg of sugar-containing chewing gum cores with peppermint taste.

Saccharose suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Drum rpm
1-2	500	45	300	11
3-12	900	45	400	11
13	600+222*	60	400	11
14-15	700	0	380	11
16-21	1000	0	380	11
22-34	1000	30	410	11
35-38	600	260	280	11
39	500	1500	290	11
40	wax powder 50g	300	300	8

* A 600g saccharose suspension + 222g peppermint oil.

Example 2

Coating in DRIA 1200 equipment of 50kg of sugar-free chewing gum cores with peppermint taste.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Drum rpm
1-2	400	0	250	11
3-5	700	15	300	11
6	700+200*	60	300	11
7-16	700	45	300	11
17-24	1000	45	350	11
25-26	700	240	240	11
27	wax powder 50g	360	360	8

* A 700g sorbitol suspension + 200g peppermint oil.

Example 3

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid eucalyptus, menthol, and anethol.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	9.9 liquid flavour	10	0	50
14	20	40	0	50
15-16	20	5	120	50
17-22	30	60	120	50
23-26	40	30	120	50
27-33	30	60	120	50
34-35	20	120	240	50
36	wax powder 2g	300	300	50

* A sorbitol suspension with 3.5% aspartame and 7.5% acesulfame K.

Example 4

Coating in DRIA 1200 equipment of 50kg sugar-containing chewing gum cores with peppermint oil encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Saccharose suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Drum rpm
1-2	500	45	300	11
3-12	900	45	400	11
13	400	10	0	11
14	400*powder	60	0	11
15-16	700	0	380	11
17	400	10	0	11
18	400*powder	60	0	11
19-20	700	0	380	11
21-24	1000	0	380	11
25-37	1000	30	410	11
38-41	700	260	280	11
42	500	1500	290	11
43	wax powder 50g	300	300	8

* A powder with a flavour concentration of 28%.

Example 5

Coating in DRIA 1200 equipment of 50kg sugar-free chewing gum cores with peppermint oil encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Drum rpm
1-2	400	0	250	11
3-5	700	15	300	11
6	350	10	0	11
7	360*powder	60	0	11
8-9	700	10	300	11
10	350	10	0	11
11	360*powder	60	0	11
12-13	700	10	300	11
14-18	700	45	300	11
19-26	1000	45	350	11
27-28	700	240	240	11
29	wax powder 50g	360	360	8

* A powder with a flavour concentration of 28%.

Example 6

Coating in tilted round kettles of 2kg sugar-free chewing gum cores with peppermint oil encapsulated in silica.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	17**powder	40	0	50
15-16	20	5	120	50
17-19	30	60	120	50
20-28	40	30	120	50
29-33	30	60	120	50
34-35	20	120	240	50
36	wax powder 2g	300	300	50

* A sorbitol suspension with 2.75% aspartame.

** A powder with a flavour concentration of 50%.

Example 7

Coating in tilted kettles of 2kg sugar-free chewing gum cores with peppermint oil encapsulated in gelatine.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	17**powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	20	10	0	50
20	17**powder	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A sorbitol suspension with 2.75% aspartame.

** A powder with a flavour concentration of 25%.

Example 8

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of eucalyptus, menthol, and anethol, encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	40**powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	20	10	0	50
20	40**powder	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A sorbitol suspension with 3.75% aspartame, and 7.5% acesulfame K.

** A powder with a flavour concentration of 24.5%.

Example 9

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of eucalyptus, menthol, and anethol, encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	20**powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	20	10	0	50
20	20**powder	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A sorbitol suspension with 3.5% aspartame and 7.5% acesulfame K.

** A powder with a flavour concentration of 24.5%.

Example 10

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid eucalyptus, menthol, and anethol, as well as menthol encapsulated in gum arabic.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	9.9 liquid flavour	10	0	50
14	20	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	20	10	0	50
20	7**powder	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A sorbitol suspension with 3.5% aspartame and 7.5% acesulfame K.

** A powder with a flavour concentration of 80%.

Example 11

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid eucalyptus, menthol, anethol, as well as ammonium chloride encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	9.9 liquid flavour	10	0	50
14	20	40	0	50
15	20	5	120	50
16-17	30	60	120	50
18	20	10	0	50
19	40**powder	40	0	50
20-21	20	5	120	50
22	20	10	0	50
23	40**powder	40	0	50
24-25	20	5	120	50
26-27	30	60	120	50
28-30	40	30	120	50
31-37	30	60	120	50
38-39	20	120	240	50
40	wax powder 2g	300	300	50

*A sorbitol suspension with 3.5% aspartame and 7.5% acesulfame K.

**A powder with a ammonium chloride concentration of 30%.

Example 12

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid eucalyptus, menthol, and powdered anise, as well as naturally extract of black pepper encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20	60	120	50
13	20	10	0	50
14	20*powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	10 liquid flavour	10	0	50
20	20	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A powder of naturally extract of black pepper in a concentration of 20%.

Example 13

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid eucalyptus, menthol, and powered anise as well as naturally basil extract encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20	60	120	50
13	20	10	0	50
14	20*powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	10 liquid flavour	10	0	50
20	20	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A powder of naturally basil extract in a concentration of 14%.

Example 14

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid eucalyptus, menthol, and powdered anise, as well as naturally thyme extract encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20	60	120	50
13	20	10	0	50
14	20*powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	10 liquid flavour	10	0	50
20	20	40	0	50
21-22	20	5	120	50
23-24	30	60	120	50
25-28	40	30	120	50
29-35	30	60	120	50
36-37	20	120	240	50
38	wax powder 2g	300	300	50

* A powder of naturally thyme extract in a concentration of 15%.

Example 15

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of mixture of liquid fruit flavours (orange, lemon, and mango) as well as citric acid encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	30**powder	40	0	50
15-16	20	5	120	50
17	20	10	0	50
18	30**powder	40	0	50
19-20	20	5	120	50
21	5.7 liquid flavour	10	0	50
22	20	40	0	50
23-24	20	5	120	50
25-26	30	60	120	50
27-30	40	30	120	50
31-37	30	60	120	50
39-40	20	120	240	50
41	wax powder 2g	300	300	50

* A sorbitol suspension with 7.5% aspartame.

** Encapsulated citric acid in a concentration of 35%.

Example 16

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid fruit flavours (orange, lemon, and mango) as well as ascorbic acid encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	30**powder	40	0	50
15-16	20	5	120	50
17	20	10	0	50
18	30**powder	40	0	50
19-20	20	5	120	50
21	5.7 liquid flavour	10	0	50
22	20	40	0	50
23-24	20	5	120	50
25-26	30	60	120	50
27-30	40	30	120	50
31-37	30	60	120	50
39-40	20	120	240	50
41	wax powder 2g	300	300	50

* A sorbitol suspension with 7.5% aspartame.

** Encapsulated ascorbic acid in a concentration of 60%.

Example 17

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of mixture of liquid fruit flavours (orange, lemon, and mango) as well as cooling agent encapsulated in gum arabic.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20*	60	120	50
13	20	10	0	50
14	20**powder	40	0	50
15-16	20	5	120	50
17	20	10	0	50
18	20	40	0	50
19-20	20	5	120	50
21	5.7 liquid flavour	10	0	50
22	20	40	0	50
23-24	20	5	120	50
25-26	30	60	120	50
27-30	40	30	120	50
31-37	30	60	120	50
39-40	20	120	240	50
41	wax powder 2g	300	300	50

* A sorbitol suspension with 7.5% aspartame.

** Encapsulated cooling agent, "Cooling Flavouring Powder" from International Flavours and Fragrances, Ltd., England, in a concentration of 20%.

Example 18

Coating in tilted kettles of 2kg sugar-free chewing gum cores with a mixture of liquid flavours (apple and cinnamon) as well as aspartame encapsulated in a 3:1 mixture of hydrogenated rape oil and carnauba wax.

Sorbitol suspension Dosage No.	Amount of dosage g	Smoothing out time sec.	Drying time sec.	Number of revolutions rpm
1	20	120	120	50
2	20	90	120	50
3	20	60	60	50
4-9	30	30	90	50
10-11	30	30	120	50
12	20	60	120	50
13	20	10	0	50
14	25*powder	40	0	50
15-16	20	5	120	50
17-18	30	60	120	50
19	6.6 liquid flavour	10	0	50
20	20	10	0	50
21-22	20	40	120	50
23-24	30	5	120	50
25-28	30	30	120	50
29-35	20	60	120	50
36-37	30	120	240	50
38	wax powder 2g	300	300	50

* Encapsulated aspartame in a concentration of 10%.

Test Results

A number of sensory tests were carried out as documentation of the achieved effect by the use of active substances in solid form in the coating of a coated chewing gum.

The tests were carried out with 5 to 8 trained tasters per test. The coated chewing gum was served in tasteless plastic cups coded with a randomised three-figure number. There was a 3-minute-break between each product tested, and each product was tested twice.

The tests were carried out partly in the form of a measurement of the flavour release as a function of time (time intensity tests), in which the products were tested after 5, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 240, 300, 420, and 540 seconds, partly in the form of determination of a taste profile, in which the products were tested in intervals; the initial phase : 0 - 1 minute, the intermediate phase 1 - 3 minute(s), and the end phase 3 - 4 minutes.

Test 1

A measurement was carried out of the flavour release as a function of time from a chewing gum coated according to Example 8, i.e. with a mixture of eucalyptus, menthol, and anethol encapsulated in fat and wax. The flavour release from this chewing gum was compared with a chewing gum coated according to Example 3, i.e. with liquid eucalyptus, menthol, and anethol. The result of the test appears from Fig. 1 which shows that the use of encapsulated flavour in the coating layer partly results in an extremely high taste onset (taste explosion) during the first 60 seconds, and partly enhances the taste in all chewing phases.

Test 2

In this test, measurement of the flavour release as a function of time by the use of the same amount of eucalyptus/menthol/anethol flavour in liquid form (Example 3) and encapsulated in fat and wax (Example 9), respectively, was carried out. The result of the test appears from Fig. 2, which shows that the use of active substance in solid

form provides a strong taste explosion in the initial phase, and a significantly enhanced effect in the first 4-5 minutes can be observed.

Test 3

In this test, the effect of addition of menthol encapsulated in gum arabic to the coating of a chewing gum coated with liquid eucalyptus, menthol, and anethol, cf. Example 10, was examined and compared with a chewing gum coated according to Example 3, i.e. only with liquid eucalyptus, menthol, and anethol.

The result of the test is shown in Fig. 3 which shows that addition of encapsulated menthol causes a strong taste explosion in the initial phase and an enhanced taste effect in all the chewing phases.

Test 4

A stability test was carried out of a chewing gum coated in accordance with Example 18, i.e. coated with apple/cinnamon flavour as well as aspartame encapsulated in fat and wax. By way of comparison, a corresponding chewing gum in which the aspartame was non-encapsulated was tested.

The result of the test is shown in Fig. 4 which shows that the chewing gum containing non-encapsulated aspartame loses its stability already after approx. 30 days after coating since it develops a bitter taste. The lack of stability is probably due to a reaction between aspartame and aldehyde-containing flavours. In a corresponding chewing gum with encapsulated aspartame in the coating no change in the taste is observed even after 90 days.

Thus, encapsulation of aspartame has a strong stability-improving effect

Test 5

A test was carried out with chewing gum coated according to Example 15, i.e. with a mixture of liquid fruit flavours (orange, lemon, and mango) as well as citric acid

encapsulated in fat and wax in order to determine the taste profile in the initial phase. By way of comparison, a taste profile was recorded for a corresponding chewing gum coated with the same fruit flavours (orange, lemon, and mango), but without encapsulated citric acid in the coating layer. The result of the test is shown in Fig. 5.

As will be apparent, a chewing gum with citric acid has a larger taste intensity and stronger citric notes than a corresponding product without citric acid.

Test 6

A test was carried out in order to determine the taste profile in the initial phase, the intermediate phase, and the end phase, respectively, of a chewing gum coated according to Example 17, i.e. with a mixture of liquid fruit flavours (orange, lemon, and mango) and with and without cooling flavour encapsulated in gum arabic. The result of the test is shown in Figs. 6, 7, and 8 which show that the chewing gum with the cooling agent has a larger taste intensity and stronger citric notes in the initial phase. As is apparent from Figs. 7 and 8, this tendency is maintained in the intermediate phase and in the end phase as well in spite of the fact that the cooling agent was placed in the coating layer only.

Thus, the chewing gum according to the invention shows an increased effect of the active substance in all the chewing phases.

Test 7

In this test the taste profile of a chewing gum coated according to Example 14, i.e. with a mixture of liquid eucalyptus, menthol, and powdered anise as well as natural thyme extract encapsulated in fat and wax, was determined.

The use of encapsulated thyme provides the possibility of developing a chewing gum with an entirely new combination of tastes without having to observe the occurrence of discoloration of the coating layer by the use of liquid extract.

Test 8

In this test the taste profile of a chewing gum coated according to Example 12, i.e. with a mixture of liquid eucalyptus, menthol, and powdered anise as well as natural extract of black pepper encapsulated in fat and wax, was determined. The result of this test is shown in Figs. 12, 13, and 14. In the same way as in test 7, the possibility of creating new combinations of tastes without discoloration of the coating layer is achieved.

The invention being thus described, it will be obvious that it may be varied in many ways. Such variations are not to be regarded as deviations from the idea and the scope of the invention, and all such modifications as would be obvious to persons skilled in the art, are intended to be included within the scope of the following claims.

Claims

1. A coated chewing gum comprising a core of chewing gum and a coating comprising a coating material and one or more active substance(s), characterised in that the active substance(s) is/are added in solid form.

2. The coated chewing gum according to claim 1, characterised in that the active substance(s) is/are selected among flavours, acids, salts, high potent sweeteners, and functional substances.

3. The coated chewing gum according to claim 1 or 2, characterised in that the flavour is selected among natural, naturally identical or synthetic flavours, and plant extracts.

4. The coated chewing gum according to any of the preceding claims wherein the active substance is a natural vegetable flavouring agent.

5. The coated chewing gum according to claim 4 wherein the natural vegetable flavouring agent is selected among fruits and herbs.

6. The coated chewing gum according to claim 5 wherein the natural vegetable flavouring agent is selected among coconut, grape fruit, orange, lime, lemon, mandarin, pineapple, strawberry, raspberry, mango, passion fruit, kiwi, apple, pear, peach, apricot, cherry, grapes, banana, cranberry, blueberry, black currant, red currant, gooseberry, and lingonberry thyme, basil, valerian, fennel, parsley, camomile, tarragon, lavender, dill, cumin, bergamot, sage, aloe vera, spearmint, peppermint, eucalyptus, and mixtures thereof.

7. The coated chewing gum according to any of claims 4-6 wherein the natural flavouring agent is dried.

8. The coated chewing gum according to claim 7 wherein the water content of the natural flavouring agent is less than 75% by weight, such as less than 60%, preferable less than 40%, more preferred less than 30%, such as less than 25%.

9. The coated chewing gum according to claim 7 wherein the water content of the natural flavouring agent is less than 20% by weight, such as less than 15%, more preferred less than 10% such as between 1.5-7%, more preferred between 2-6%.

10. The coated chewing gum according to any of claims 4-9 wherein the natural flavouring agent is freeze-dried.

11. The coated chewing gum according to any of claims 4-10 wherein the natural flavouring agent is in the form of a powder, slices or pieces or combinations thereof.

12. The coated chewing gum according to claim 11 wherein the natural flavouring agent is in a form where the particle size is less than 3mm, such as less than 2mm, more preferred less than 1mm, calculated as the longest dimension of the particle.

13. The coated chewing gum according to claim 11 wherein the natural flavouring agent is in a form where the particle size is from about 3μ to 2mm, such as from 4μ to 1mm.

14. The coated chewing gum according to any of claims 4-14 wherein the natural flavouring agent comprises seeds from a fruit e.g. from strawberry, blackberry and raspberry, and which seeds are substantially intact.

15. The coated chewing gum according to any of the preceding claims wherein the natural vegetable flavouring agent also provides the gum formulation with natural colour.

16. The coated chewing gum according to claim 3, characterised in that the flavour is selected among peppermint, periwinkle, eucalyptus, spearmint, anethol, menthol, powdered anise, and fruit flavours such as orange, lemon, mango, pineapple, lime,

strawberry, cherry, black currant, blueberry, raspberry, wild berry, cranberry, apple, pear, banana, prune, and plum flavour.

17. The coated chewing gum according to claim 3, characterised in that the plant extracts are selected among extracts of liquorice, coffee, tea, herbs such as sage, thyme, basil, bergamot, balm, valerian, camomile, lavender, aloe vera, and spices such as pepper, cinnamon, capsicum, paprika, tarragon, fennel, mustard, dill, caraway, parsley, and tomato.

18. The coated chewing gum according to claim 2, characterised in that the acids are selected among citric acid, malic acid, tartaric acid, lactic acid, and ascorbic acid.

19. The coated chewing gum according to claim 2, characterised in that the salts are selected among sodium chloride, potassium chloride, ammonium chloride, sodium bicarbonate, and carbamide.

20. The coated chewing gum according to claim 2, characterised in that the sweeteners are selected among aspartame, acesulfame K, saccharin, cyclamate, neohespiridine, thaumatin, glycyrrhizin, and salts thereof, monellin, sucrolase, and alitame.

21. The coated chewing gum according to claim 2, characterised in that the functional substances are selected among vitamins, "cooling agents", flavour enhancers, and pharmaceuticals in the coating such as the vitamins A, B, C, D, and E, enzymes, nicotine, caffeine, acetylsalicylic acid, chlorhexidine, zinc compounds, and antihistamines.

22. The coated chewing gum according to any of the preceding claims wherein the active substance(s) is/are in an encapsulated form.

23. The coated chewing gum according to any of the preceding claims wherein the encapsulated active substance is encapsulated in one or more material(s) selected among fatty substances, waxes, gelatine, gum arabic, starch, cellulose, cellulose derivatives, shellac, polyvinyl acetate, polyethylene, casein, zein, B cyclodextrine,

silica, yeast cells, and a mixture of the above encapsulation materials, preferably a mixture of fatty substances and carnauba wax.

24. The coated chewing gum according to any of claims 1-23, characterised in that the coating additionally comprises one or more liquid active substance(s).

25. A method for the preparation of a coated chewing gum according to any of claims 1-24, characterised in that it comprises the following steps:

1) preparation of a core of chewing gum in a manner known *per se*,

2) preparation of a coating suspension, also in a manner known *per se*,

3) application of the coating suspension onto the cores of chewing gum in a manner known *per se*,

4) Applying on the coating of one or more active substance(s) in solid form in one or more increment(s) after the application of the coating suspension, and optionally repeating step 3) and 4)

5) optionally, application of one or more liquid active substance(s) in one or more increment(s) between the applications of the coating suspension,

6) optionally, finally application of a surface layer.

26. The method according to claim 25, characterised in that the coating suspension comprises an aqueous solution of a sugar, a sugar alcohol, an artificial sweetener or mixtures thereof.

27. The method according to claim 26, characterised in that the coating suspension comprises an aqueous solution of one or more constituent(s) selected among saccharose, dextrose, sorbitol, xylitol, tagatose, mannitol, maltitol, isomalt, aspartame, acesulfame K, saccharine, cyclamate, taline, and neohespiridine.

28. The method according to any of claims 25-27, characterised in that the coating suspension is applied in approx. 2 to 90 increments, preferably in approximately 30-60 increments.

29. The method according to any of claims 25-28, characterised in that the active substance(s) present in solid form is/are applied in 1 to 10 increment(s) between the dosages of the coating suspension, preferably 1-4 increment(s).

30. The use of one or more active substance(s) in solid form in the coating of a coated chewing gum to achieve a fast onset of the effect.

31. The use of one or more active substance(s) in solid form in the coating of a coated chewing gum to achieve a better stability of the active substance.

32. The use of one or more active substance(s) in solid form in the coating of a coated chewing gum to achieve an increased effect of the active substance(s) in all chewing phases.

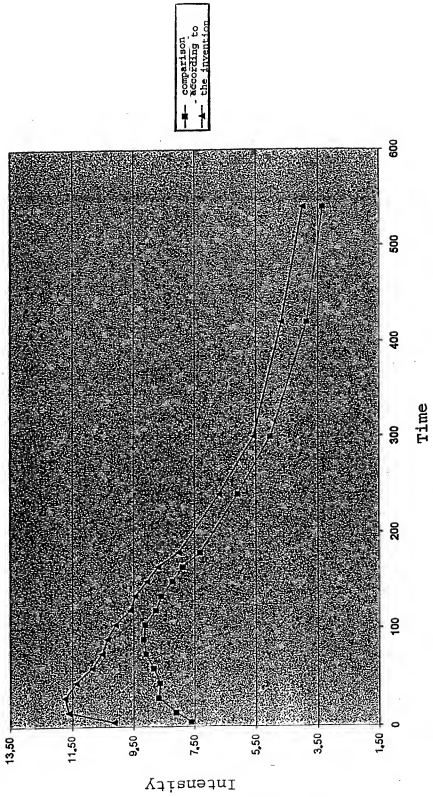

comparison according to the invention
Intensity
13,50
11,50
9,50
7,50
5,50
3,50
1,50
0
100
200
300
400
500
600
Time

Fig. 1

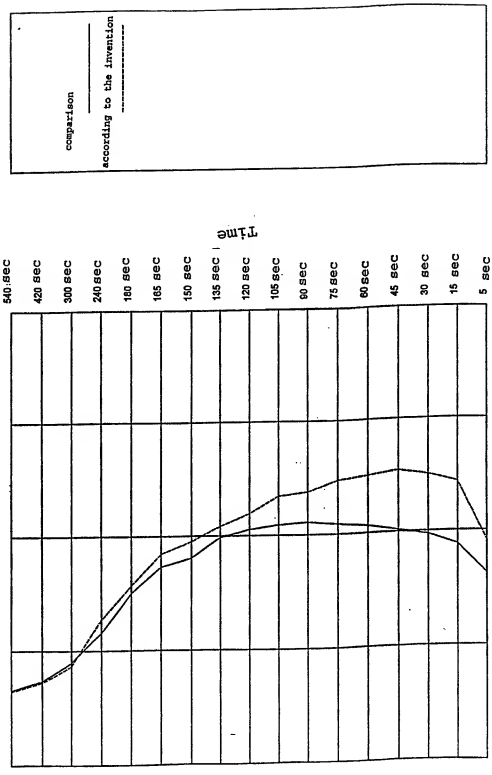

comparison
according to the invention
Time
540 sec
420 sec
300 sec
240 sec
180 sec
165 sec
150 sec
135 sec
120 sec
105 sec
90 sec
75 sec
60 sec
45 sec
30 sec
15 sec
5 sec
0
3,8
7,5
11,3
15
Intensity

Fig. 2

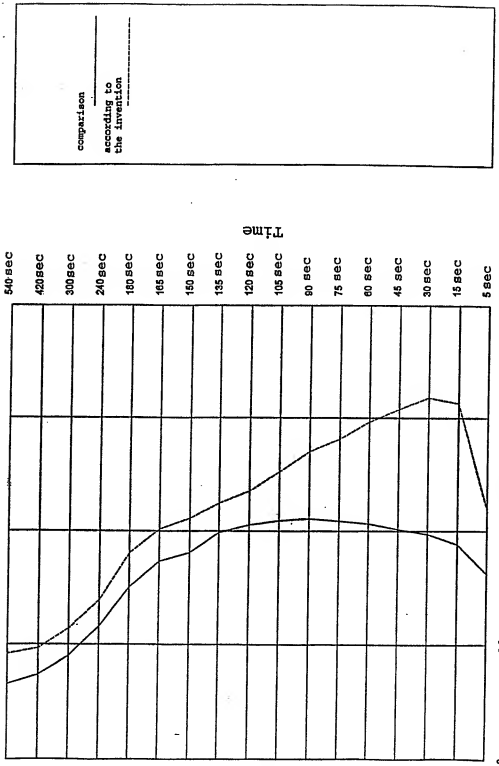

comparison
according to the invention
Time
540 sec
420 sec
300 sec
240 sec
180 sec
165 sec
150 sec
135 sec
120 sec
105 sec
90 sec
75 sec
60 sec
45 sec
30 sec
15 sec
5 sec
0
3.8
7.5
11.3
15
Intensity

Fig. 3

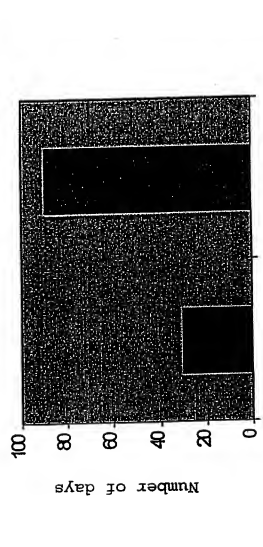

Stability
Number of days
100
80
60
40
20
0
Non-encapsulated aspartame
Encapsulated aspartame

Fig. 4

comparison according to the invention
Start phase
Astringent 1
Flavour intensity
Time before taste
Initial softness
Biting
Softness
Sweetness
Juicy
Astringent 2
Mango
Citrus
Bitter
Cooling
Scale
0
3.75
7.50
11.25
15

Fig. 5

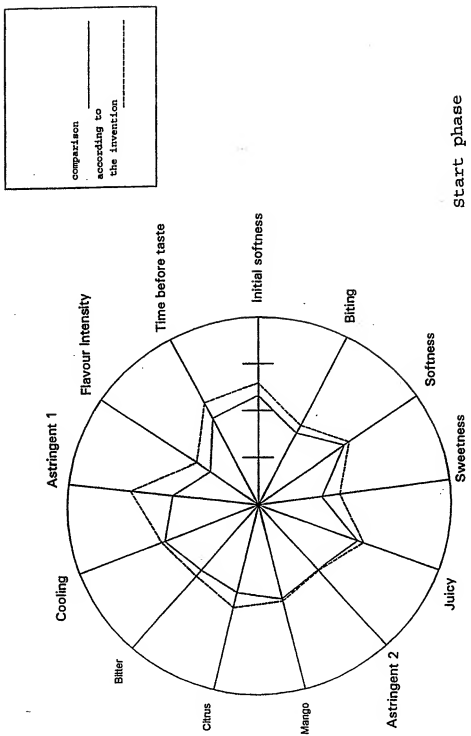

comparison
according to
the invention
Start phase
Initial softness
Biting
Softness
Sweetness
Juicy
Astringent 2
Mango
Citrus
Bitter
Cooling
Astringent 1
Flavour Intensity
Time before taste
Scale :
0
3.75
7.50
11.25
15

Fig. 6

comparison
according to
the invention
Intermediate phase
Flavour intensity
Softness
Biting
Softness
Sweetness
Juicy
Astringent 2
Mango
Citrus
Bitter
Cooling
Astringent 1
Scale:
0
3.75
7.50
11.25
15

Fig. 7

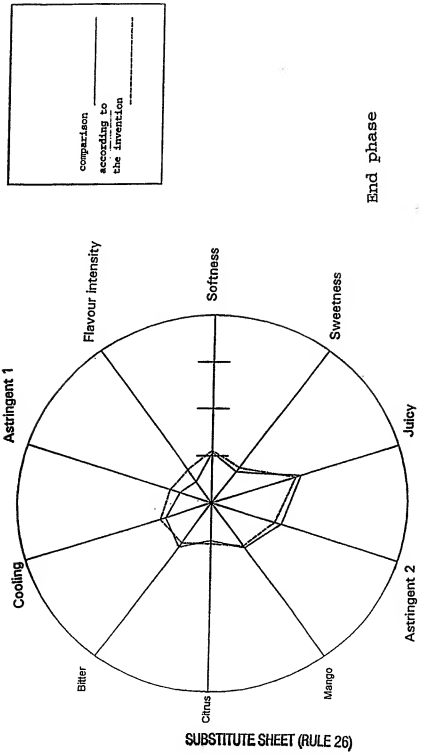
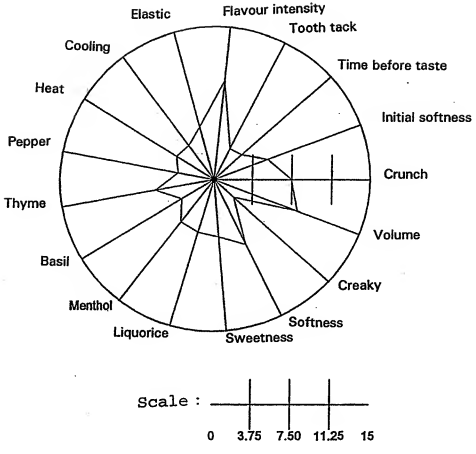
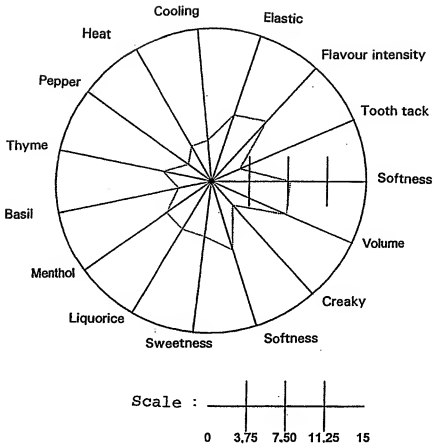

comparison according to the invention
End phase
Astringent 1
Flavour intensity
Softness
Sweetness
Juicy
Astringent 2
Mango
Citrus
Bitter
Cooling
Scale:
0
3,75
7,50
11,25
15

Fig. 8



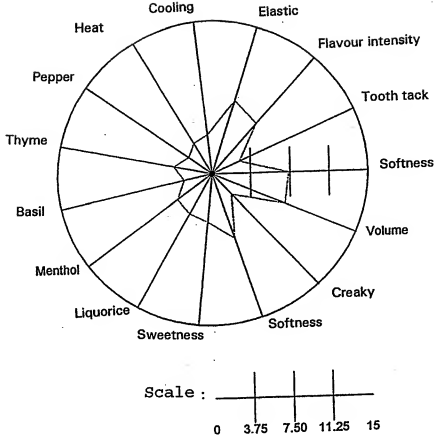
Start phase

Fig. 9



Intermediate phase

Fig. 10



End phase

Fig. 11

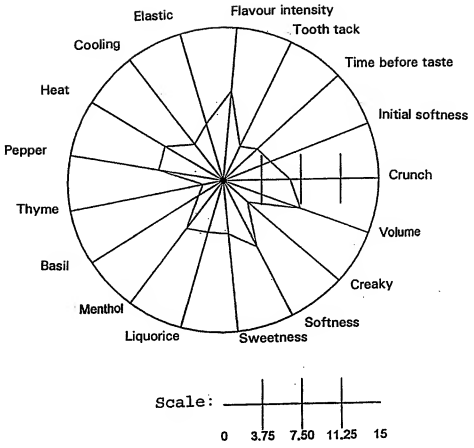
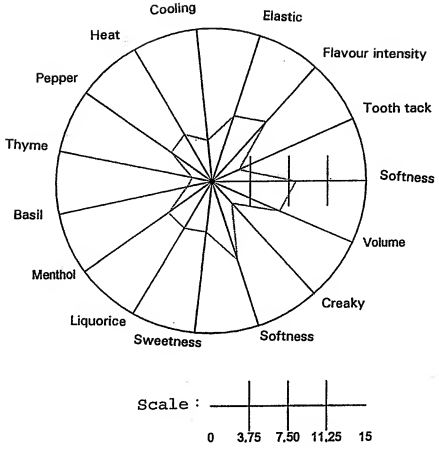
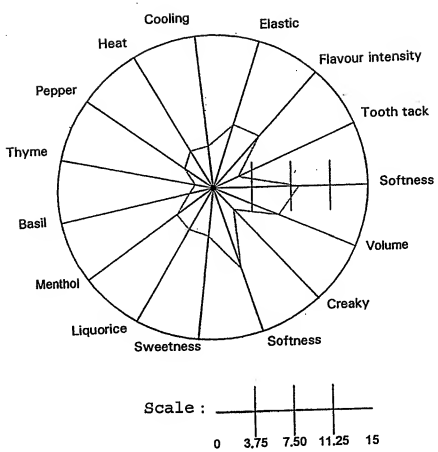

Elastic
Flavour intensity
Tooth tack
Cooling
Time before taste
Heat
Initial softness
Pepper
Crunch
Thyme
Volume
Basil
Creaky
Menthol
Softness
Liquorice
Sweetness
Scale:
0 3.75 7.50 11.25 15
Start phase

Fig. 12



Intermediate phase

Fig. 13



End phase

Fig. 14

INTERNATIONAL SEARCH REPORT

Internatio ›pplication No
PCT/DK 99/00108

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23G3/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A23G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 263 224 A (WARNER-LAMBERT COMPANY) 13 April 1988 see claims; examples	1,2,19, 21,24-32
X	US 4 250 195 A (CHERUKURI ET AL.) 10 February 1981 see line 1 - line 30 see column 6, line 33-36; examples	1-9, 11-13, 15-17, 25-32
X	EP 0 435 698 A (WM WRIGLEY JR. COMPANY) 3 July 1991 see page 1, line 13 - line 22 see page 2, line 25 - line 27	1-3,16, 20,22-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1999	14/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lepretre, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic application No
PCT/DK 99/00108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		PH 27260 A	04-05-1993

RELATED PROCEEDINGS APPENDIX

None.